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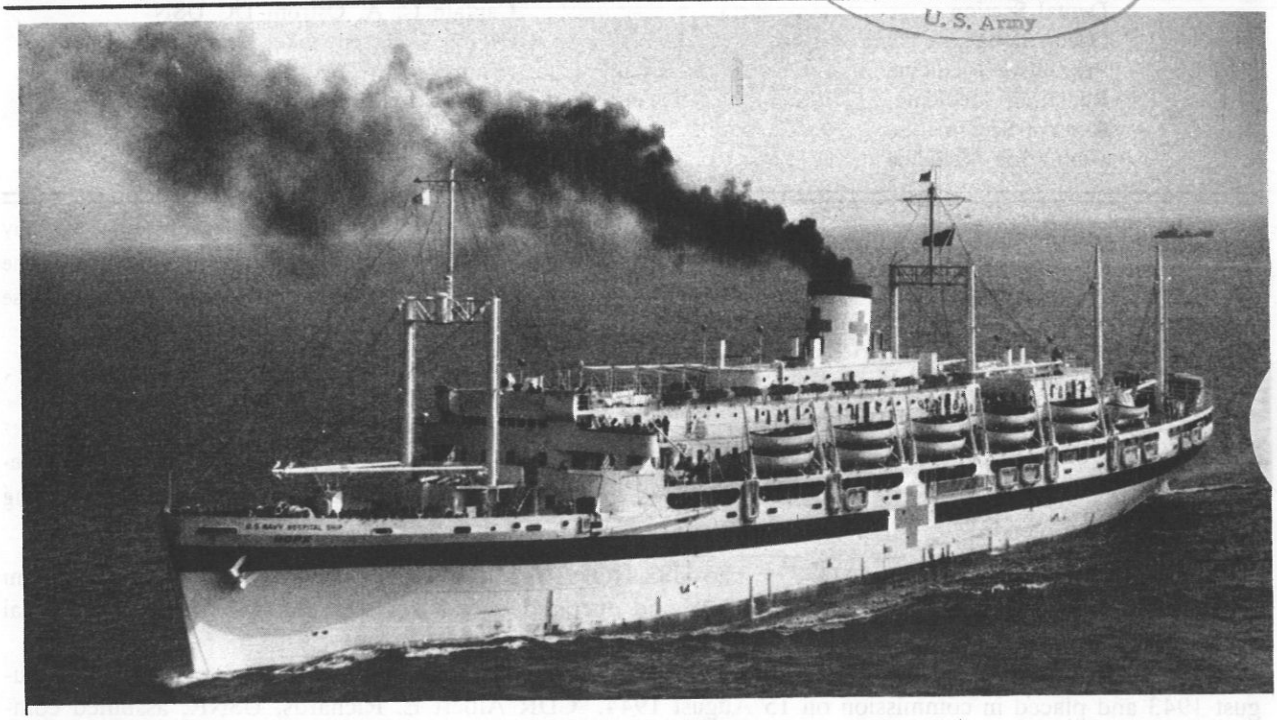

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Policy

The U.S. Navy Medical News Letter is basically an official Medical Department publication inviting the attention of officers of the Medical Department of the Regular Navy and Naval Reserve to timely up-to-date items of official and professional interest relative to medicine, dentistry, and allied sciences. The amount of information used is only that necessary to inform adequately officers of the Medical Department of the existence and source of such information. The items used are neither intended to be, nor are they, susceptible to use by any officer as a substitute for any item or article, in its original form. All readers of the News Letter are urged to obtain the original of those items of particular interest to the individual.

Change of Address

Please forward changes of address for the News Letter to Editor: Bureau of Medicine and Surgery, Navy Department, Washington, D.C. 20390 (Code 18), giving full name, rank, corps, and old and new addresses.

FRONT COVER: USS HOPE (AH–7). The USS HOPE was one of three hospital ships converted from 6,000 ton Maritime hull and fitted with 680 beds and operated by a Navy crew but with an Army hospital unit on board.

Built by the Consolidated Steel Corporation at Wilmington, California, the vessel was acquired on 30 August 1943 and placed in commission on 15 August 1944. CDR Albert E. Richards, USNR, assumed command of the ship, and LCOL Thomas B. Protzman, MC, USA, assumed command of the hospital.

After her shakedown, the ship sailed from San Pedro, California on 23 September for Pearl Harbor. Then the ship set course for Guadalcanal, however, she was diverted to Manus Island and arrived on 17 October 1944, only to find that the fleet had already left for the invasion of the Philippines.

Arriving in Leyte Gulf on 7 November 1944, the HOPE admitted 447 patients. After waiting for two days in an effort to get an additional 200 wounded aboard, she sailed on 9 November.

Her patients were discharged at Hollandia, New Guinea, and the ship sailed again for Leyte via Kossol Passage, arriving in Leyte Gulf on 23 November. Embarking 602 patients, she departed the same day for Hollandia. Taking aboard 120 nurses, she departed again on 30 November for the Philippines.

During the morning of 3 December lookouts spotted smoke which was presumed to be from a sub equipped with "Schnorkel" apparatus shadowing the HOPE. Six hours later, a Japanese torpedo plane made an attack in spite of the ship's clear markings. Fortunately the attack was unsuccessful.

Discharging her patients at Manus, the ship picked up 708 wounded and took them to Hollandia. During the return voyage distress signals were picked up on Christmas Day and following the radio beam, the ship picked up four Army flyers who had crashed 30 hours before.

This ship had an overall length of 416 feet, beam of 60 feet, speed of 14 knots, displacement of 6,000 tons and a crew of 20 officers and 213 men.

The issuance of this publication approved by the Secretary of the Navy on 4 May 1964.

PENICILLIN ANTIBODY AS A CAUSE OF POSITIVE DIRECT ANTIGLOBULIN TESTS

Edwin M. Clayton MD, John Altshuler MD and Joseph R. Bove MD. Departments of Pathology and Medicine, Yale University School of Medicine, and the Yale-New Haven Hospital, New Haven, Connecticut.* *Amer J Clin Path 44(6): 648–653, December 1965. Permission granted by The Williams & Wilkins Co.*

In 1958 Ley and associates described antibodies in the serum of individuals who had previously received penicillin. These antibodies reacted only with penicillin-coated cells and could be neutralized by prior incubation of the patient's serum with penicillin. Penicillin antibodies have also been reported to cause positive direct antiglobulin tests. The present report describes 4 additional patients with a positive-direct antiglobulin test from penicillin antibodies.

Report of Cases

Case 1. Several months before admission a 54-year-old man with rheumatic mitral valvular disease had been treated with penicillin for subacute bacterial endocarditis.

When admitted to the Yale-New Haven Hospital, his hematocrit value was 36 percent. Microaerophilic β-hemolytic streptococci were cultured from his blood on 8 occasions, and intravenous treatment with 20 million units of penicillin a day was begun. Sixteen days later his hematocrit value was 27 percent and his reticulocyte count 4.6 percent. On the 25th day of therapy a positive direct antiglobulin test (3+) was found. Because antiglobulin testing of the patient's serum and eluate failed to show a blood group antibody, a penicillin antibody was suspected. Its presence was confirmed by finding in his serum an antibody that reacted only with penicillin-coated cells and by eluting a similar antibody from his own erythrocytes.

Penicillin therapy was administered for a total of 6 weeks. He had no allergic reactions but eosinophil counts as high as 14 percent were recorded. When therapy was stopped, his direct antiglobulin test was still strongly positive (4+) but his hematocrit value had stabilized at 30 percent. He had not been transfused.

Two months after discharge he was readmitted because of recurrent subacute bacterial endocarditis. Because on this admission Klebsiella-Aerobacter was identified in blood cultures, penicillin was not given. His direct antiglobulin test was positive (2+) on this admission but negative 6 weeks later.

He has remained well since discharge.

Case 2. This 73-year-old woman was admitted because of fever for 8 days. A systolic murmur was heard at the apex of the heart. Her hematocrit value was 31 percent, hemoglobin 9.7 Gm per 100 ml, and reticulocyte count 1.5 percent.

On 6 occasions enterococci were cultured from her blood, and a diagnosis of subacute bacterial endocarditis was made. Twenty million units of penicillin intravenously were given daily. She developed an erythematous, slightly papular rash 3 days after penicillin had been started. A drug reaction was suspected, but penicillin was continued for 21 days. At the end of therapy her direct antiglobulin test was strongly positive (4+). Penicillin antibodies were found in her serum and in eluates prepared from her erythrocytes. Her hematocrit value was 35 percent and leukocyte count 5850 per cu mm with 33 percent eosinophils.

Case 3. This 47-year-old woman was admitted because of fever and lethargy. Septicemia was suspected and confirmed when 6 blood cultures showed Group A β-hemolytic streptococci. Daily antibiotic therapy consisted of i.m. streptomycin and tetracycline and 20 million units of penicillin i.v. The penicillin was discontinued after 3 days, but the other antibiotics were continued. Beginning on the ninth hospital day 2.4 million units of penicillin i. m. were given daily for 3 days. Two weeks later her direct antiglobulin test was strongly positive (4+). Her hematocrit value had dropped from 38 percent on admission to 25 percent. Penicillin antibody was found in her serum and eluted from her sensitized erythrocytes. A red cell survival study was made and showed a Cr^{51} half time of 16 days (normal 28 to 32 days). The patient improved gradually. The maximal reticulocyte count observed was 3.4 percent.

Case 4. This 52-year-old woman had rheumatic heart disease with mitral stenosis. In 1959, 4 years before the present admission, she had a mitral valvulotomy with relief of heart failure. She had received penicillin and had taken 250,000 units of oral penicillin V daily ever since.

Because of frequent attacks of pulmonary edema the patient was readmitted in January 1964, and a

* LCDR MC USNR.

Starr-Edwards valve inserted. Before operation her direct and indirect antiglobulin tests were negative.

Two weeks postoperatively she developed fever and splinter hemorrhages. The diagnosis of subacute bacterial endocarditis was made despite negative blood cultures. Initially she was administered 20 million units of penicillin a day intravenously. The dose was increased to 30 million units a day 4 days later. After a total of 120 million units of penicillin i. v. had been given, her direct antiglobulin was found to be positive (2+) and her indirect antiglobulin test negative. After 5 additional days of penicillin therapy the direct antiglobulin test had become stronger (3+). Her reticulocyte count was 8.0 percent and hematocrit value 35 percent. Serum and eluate showed a penicillin antibody.

Further cultures of her blood demonstrated a yeast septicemia. Penicillin was discontinued, and amphotericin B begun. The patient developed *Staphylococcus aureus* septicemia and died 2 months after surgery. At autopsy endocarditis was found at the Starr-Edwards valve suture line. An unidentified yeast and *S. aureus* were cultured from the site.

METHODS

Identification of Penicillin Antibody

Group O bloods were drawn into ACD Vacutainer tubes.* Buffered potassium penicillin G was dissolved in 0.9 percent saline solution so that the concentration was 200,000 units per ml. One half milliliter of this solution was added to 3.5 ml of ACD blood, yielding a final concentration of 25,000 units per ml of blood. To a second aliquot of blood, saline solution was added as a control. Both bloods were incubated at 37 C for 1 hr and then placed in a refrigerator overnight before use. The penicillin-coated cells were satisfactory for several weeks and were discarded when moderate hemolysis was observed. Before use they were washed with 0.9 percent saline solution 4 times. All serums were tested in parallel with the penicillin-coated and control cells. In a positive reaction agglutination was observed only with the penicillin treated cells.

* S 3204X, Formula 16, 0.7 ml ACD solution (Formula B).

Neutralization Experiments

Doubling dilutions of serum were made with 0.9 percent saline solution. Penicillin solutions containing 1,250; 2,500; 5,000; 10,000; 20,000; and 50,000 units per 0.1 ml were prepared by diluting penicillin G in 0.9 percent saline solution. To 0.1 ml of each dilution of serum an equal volume of diluted penicillin was added in a 10- by 75-mm tube. These were incubated at room temperature for 30 min, after which 0.1 ml of a 4 percent suspension of penicillin-coated cells was added. The mixture was placed at 37 C for 1 hr, washed thrice in 0.9 percent saline solution, and tested with antiglobulin serum.

Elutions

The method of Landsteiner was used. After washing 3 or 4 times the erythrocytes were suspended in an equal volume of 0.9 percent saline solution. The resulting suspension was agitated gently for 5 min at 56 C, centrifuged, and the supernatant quickly removed.

Table 1
Penicillin Antibody Titers*

Case No.	Test	I.S.†	37C‡	Antiglobulin Test	Direct Antiglobulin Test
1	Initial	4	2	64	4†
	5 mo later	2	2	16	Neg
2	Initial	64	256	1,024	4†
3	Initial	8	16	512	4†
	5 mo later	2	2	32	Neg
4	Before penicillin treatment	1	4	128	Neg
	During treatment	1	4	128	3†
	2 wk after treatment	8	8	128	2†

* Titer results are reported as the reciprocal of the serum dilution giving a 2 † reaction.
† Immediate spin.
‡ One hour's incubation.

TABLE 2.—Inhibition of Penicillin Antibodies *

Case No.	Units of Penicillin						
	None	1,250	2,500	5,000	10,000	20,000	50,000
1	128	128	64	32	4	2	0
2	1,024	†	256	256	256	128	16
3	256	†	64	64	32	2	1
4	128	†	64	32	16	8	8

* Results recorded are the reciprocals of the antibody titers after incubation of serums with different concentrations of penicillin.
† Titer not performed.

In Vivo Penicillin Coating of Erythrocytes

Nine patients receiving penicillin were studied to determine if penicillin coating of erythrocytes occurred in vivo. None of these patients had penicillin antibody. Blood was collected at intervals during treatment, the erythrocytes washed thrice with 0.9 percent saline solution, and incubated with serum from Case 1. Sensitization was determined by means of the antiglobulin method.

RESULTS

Serologic Studies

Titers of the penicillin antibody in the serum of each of the 4 patients are listed in Table 1.

Table 2 is a summary of data obtained from the neutralization experiments. Complete neutralization of neat serum was achieved in only 1 of the antibodies. In the other cases only partial neutralization occurred despite penicillin concentrations of 50,000 units per 0.1 ml of serum.

In Vivo Penicillin Coating

Prior to treatment with penicillin i.v. in Case 4, serum contained penicillin antibody at a titer of 1:128. This was probably due to her prolonged treatment with low doses of penicillin. The direct antiglobulin test was, however, negative. Nine days after intravenous therapy with high doses of penicillin the direct antiglobulin test became positive (2+), although the serum antibody titer remained the same.

In vivo coating of erythrocytes was also demonstrated in 2 patients receiving large doses of intravenous penicillin. Coating could not be shown after oral or intramuscular therapy (Table 3).

Table 3
Demonstration of In Vivo Coating of Erythrocytes in Patients Receiving Penicillin

Patient No.	Type of Penicillin	Daily Dose	Duration	Route	Demonstration of Erythrocyte Coating
1	Methicillin	6Gm	30	p.o.	No
2	Nafcillin	1Gm	5	i.v.	No
3	Penicillin G	5 million units	10	i.v.	No
4	Penicillin G	20 million units	4	i.v.	No
5	Penicillin G	20 million units	10	i.v.	2+ day 10
6	Penicillin G	20 million units	11	i.v.	2+ day 8 3+ day 11
7	Penicillin G	1.2 million units	10	i.m.	No
8	Penicillin G	0.6 million units	2	i.m.	No
9	Penicillin G	20 million units	4	i.v.	No

TABLE 4

DIRECT ANTIGLOBULIN TESTS (AGT) DUE TO PENICILLIN ANTIBODY: SUMMARY OF REPORTED CASES

Reference	Illness	Penicillin Therapy	Serologic Findings		Allergic Manifestations	Course	Evidence of Abnormal Hemolysis
			Serum AGT titer	Direct AGT			
Ley, Cahan, and Meyer	Not stated	1.8×10^6 units q.d. and 1.8×10^7 units q.d.	Not stated	Strongly positive	Not stated	Developed anemia, required transfusions; patient died	
Strumia and Raymond	S.B.E.	2.4×10^7 units q.d. i.m. 27 days	1:32	Positive	Urticaria, rash	Patient well 18 mo. after acute illness; however, penicillin antibody present at 1:4 titer	Hb. fell from 12.2 to 6.2 Gm./100 ml., reticulocyte count 15%, spherocytes on peripheral smear, Cr^{51}, $t_{1/2}$ of 10 days
Beardwell	S.B.E.	1×10^7 units q.d. $\times$ 26 days	1:400	1:256 Positive	Eosinophilia 30%	Hb. and reticulocyte count returned to normal after cessation of therapy, and direct antiglobulin test became negative 3 mo. after acute illness	"Red cell survival time shortened," reticulocyte count 15.2%
Van Arsdel and Gilliland, Case 1	S.B.E.	2.0×10^7 units q.d. i.v. $\times$ 18 days	1:512	Strongly positive	None	Developed anemia, required transfusion, recovered from acute illness, and died 1 year later from congestive heart failure	Reticulocyte count 5.5%; hematocrit fell from 27% to 20%
Van Arsdel and Gilliland, Case 2	Staphylococcus septicemia and probable endocarditis	3.0×10^7 units q.d. i.v. $\times$ 21 days	1:512	Strongly positive	None	Developed anemia, required transfusions; recovered	Reticulocyte count 5%; hematocrit fell from 40% to 20%
Present report, Case 1	S.B.E.	2×10^7 units q.d. i.v. $\times$ 42 days	1:64	4+	Eosinophilia 14%	No transfusions needed, direct Coombs test negative 5 mo. later	Hct. fell from 36% to 27%; reticulocyte count 4.6%
Present report, Case 2	S.B.E.	2×10^7 units q.d. i.v. $\times$ 21 days	1:1024	4+	Rash, eosinophilia 33%	No transfusions	None; hematocrit rose from 31% to 35% during therapy
Present report, Case 3	Septicemia	2×10^7 units q.d. $\times$ 3 days 2.4×10^6 units q.d. i.m. $\times$ 3 days	1:512	4+	None	No transfusions; hematocrit returned to normal after treatment stopped	Hematocrit fell from 38% to 25%, reticulocyte count 3.4%; Cr^{51} $t_{1/2}$ of 16 days
Present report, Case 4	Suspected S.B.E.	2 to 4 $\times 10^7$ units q.d. i.v. for 11 days	1:128	3+	None	Required 5 units blood to maintain hematocrit; died	Hematocrit fell; reticulocytes 8.0%

Discussion

A positive direct antiglobulin test in a hospitalized patient is of great importance and may signify acquired hemolytic anemia. Such a finding is uncommon, even in the largest of medical centers, and always warrants detailed investigation of the patient and his disease. The 4 patients reported here had positive direct antiglobulin tests due to penicillin antibody and in vivo penicillin coating of their own erythrocytes. All were seen within 15 months and were perplexing because, despite a strong direct reaction, the indirect antiglobulin tests were persistently negative. In addition, antiglobulin testing of eluates from their in vivo coated cells were consistently negative. These findings led us to suspect penicillin antibody as the cause of the abnormal serology, a suspicion confirmed by substituting penicillin-coated erythrocytes for Group O screening cells in the indirect antiglobulin tests of serums and eluates. A few case reports of similar patients have appeared since the original one in 1958. Findings of the previously reported cases and the 4 presented here are in Table 4. In all, large doses of penicillin were given, usually intravenously, as therapy for subacute bacterial endocarditis or septicemia. From the cases reported so far it seems that the size of the dose is important. Fundenberg and German were unable to show in vivo coating of erythrocytes when 6 million units of penicillin were given parenterally. In order to get more data on this point 9 patients receiving penicillin were studied by us (Table 3). In 2 of these in vivo penicillin coating could be demonstrated at 8 and 10 days after penicillin in doses of 20 million units i. v. daily. The other 7 remained negative. In Case 4 in vivo coating was also demonstrated after a total dose of 120 million units i. v. It appears from our study that large doses of penicillin are important for in vivo penicillin coating.

All previously reported patients were found during the evaluation of unexplained anemia, and the authors emphasized the direct antiglobulin test from penicillin antibodies as a cause of hemolytic anemia. The present 4 cases cover a wider spectrum. In Case 4 hemolysis was prominent and transfusions were given. The anemia in Cases 1 and 3 was not severe enough to require replacement of blood. In contrast, in Case 2 there was no evidence of hemolytic anemia although the antiglobulin test was strongly positive, and the antibody had a high titer. Thus, the penicillin antibodies may or may not be responsible for shortened erythrocyte survival.

The presence of penicillin antibody does not seem to interfere with in vitro compatibility testing and the safe administration of blood. It is likely, however, that the transfused red cells will eventually become penicillin-coated if antibiotic therapy is continued, and may also undergo increased hemolysis. In addition, the positive direct antiglobulin test may cause confusion in the minor crossmatch.

None of the patients exhibited allergic reactions sufficiently severe to require termination of therapy. Four, however, developed urticaria, rash, or eosinophilia. Because of the life-threatening process being treated, therapy was continued without adverse effect. The allergic manifestations of penicillin may be caused by penicillin antibody different from the one responsible for hemolytic anemia and the positive direct antiglobulin test.

Van Arsdel and Gilliland have suggested that those penicillin antibodies responsible for allergy are neutralized with ease, whereas those causing hemolytic anemia are extremely difficult to inhibit. The antibody in all patients in the present study was difficult to neutralize, and if their theory is correct, our patients might have had mild hemolysis undetected by the tests used. An erythrocyte survival in 1 patient was, in fact, short; however, it is not clear whether this was due to the antibody or the underlying disease.

The last patient studied (Case 4) developed a direct antiglobulin test due to penicillin antibody after the replacement of her mitral valve with a Starr-Edwards prosthesis. Although she clearly developed this test after a course of penicillin i. v., she might have been erroneously classified as a patient with autoimmune hemolytic anemia as a complication of Starr-Edwards valve replacement. These patients also have a positive direct antiglobulin test.

A search for penicillin antibodies should be included in the investigation of unexplained positive direct antiglobulin tests, especially if the patient has recently received penicillin. A positive direct antiglobulin test caused by penicillin antibodies is not infrequent, and investigation of the problem is within the ability of any transfusion service.

Summary

Four patients with positive direct antiglobulin tests caused by in vivo penicillin-coating of their own erythrocytes followed by sensitization with penicillin antibody are reported. Penicillin readily coats cells in vitro and allows a simple test to be performed for the detection of penicillin antibody. All blood transfusion services should be prepared to undertake this investigation.

RECURRENT PSEUDOTUMOR CEREBRI IN PREGNANCY

Report of 2 Cases

Charles W. Nickerson LCDR MC USN and Robert F. Kirk CDR MC USN, FACOG. Obstetrics-Gynecology 26(6):811–813, December 1965.

Pseudotumor cerebri, sometimes known as benign, intracranial hypertension, is a syndrome characterized by increased intracranial pressure in the absence of a space-occupying lesion or internal hydrocephalus. There are few references in the literature which mention or document occurrences of this condition during pregnancy. Greer recently reported a small series of cases diagnosed early in pregnancy with a follow-up of each pregnancy, but there are very few reports of long-term follow-ups in subsequent pregnancies of patients with this relatively uncommon disease. Presented in this paper are case reports of 2 patients with recurrent pseudotumor cerebri during pregnancy.

Case Reports

Case 1. (P.H. 397912) A 23-year-old Negro gravida 4 para 3, had had her LMP Apr. 19, 1963. She was admitted in November 1963 for evaluation of headaches, photophobia, and blurring of vision in the right eye of 1 month's duration. Her past history revealed that she had been in apparent good health until the fourth month of her third pregnancy in May 1962. At that time she developed headaches and blurred vision. Neurologic and ophthalmologic consultations established the diagnosis of pseudotumor cerebri. A right cerebral angiogram was normal. She was delivered of a normal 6-lb infant in September 1962, with gradual resolution of her symptoms and papilledema. However, she felt that her vision did not return to normal.

In the present pregnancy, results of physical examination were normal for 16 weeks gestation except for bilateral early papilledema. Spinal fluid analysis and all laboratory test results were normal except for an opening spinal fluid pressure of 278 mm water. Bilateral enlargement of the physiologic blind spot was demonstrated on tangent-screen testing. She was treated with 500 mg chlorthiazide daily and 300 mg potassium chloride, t. i. d. After 2 weeks hospitalization she had marked symptomatic improvement, with clearing of the papilledema but with no decrease in the area of the blind spot. She was discharged home under therapy.

She was readmitted Jan. 8, 1964, at which time she had only occasional complaints of blurred vision, light-headedness, and weakness. Physical examination was not remarkable except for a blood pressure of 140/80 and the appearance of small microaneurysms about the left optic disc. No papilledema was found and all laboratory test results were within normal limits.

On the twelfth hospital day she spontaneously commenced labor and delivered a normal 5-lb. 12-oz. infant. The day following delivery a Pomeroy-type tubal ligation was performed. Sterilization had been recommended by the departments of neurology and opthalmology to prevent further loss of vision, which had progressed during the two observed pregnancies. She was asymptomatic with results of physical examination normal at her 6 weeks postpartum examination.

Case 2. (H.M. 740998) A 24-year-old caucasian gravida 5 para 2, abortus 2, had had her LMP Feb. 25, 1964. She was admitted on July 27, 1964, for evaluation. During her third pregnancy, in 1959, a diagnosis of pseudotumor cerebri was made following a complete neurosurgical evaluation including angiograms, ventriculograms, and cerebral decompression by temporal burr holes. After decompression she had one uneventful pregnancy and delivery in 1960 and an early spontaneous abortion in 1962. Six months following the abortion she was admitted in a nongravid state for evaluation. There were no abnormal findings at that time.

On admission she had no complaints. Physical examination and laboratory results were normal except for mild bilateral papilledema and moderately tense, pulsating burr holes. The neurosurgical consultant found her condition to be unchanged from her pre-pregnant state. The ophthalmologist found her normal except for a slightly increased left physiologic blind spot. She was treated with a low sodium diet and was discharged on July 30, 1964, to be followed in the prenatal clinic. She had an uneventful prenatal course and, on Nov. 10, 1964, she was delivered under pudendal block anesthesia of a normal, 7-lb. 8-oz. infant. On the second postpartum day a Pomeroy-type tubal ligation was performed under general anesthesia. She made an uneventful recovery, and examination was unremarkable at 2 and 6 weeks postpartum.

Discussion

Frequent symptoms found in association with the condition are headache, decreased visual acuity, diplopia, and occasional tinnitus. There is no disturbance of consciousness or intellect and seizures

have not been reported. The most striking physiologic finding is bilateral papilledema. Focal neurologic signs are absent except for possible abducens nerve palsy. The cerebrospinal fluid pressure is increased but fluid is normal. Ventriculography reveals normal or slightly small ventricles.

The prognosis is generally good, with the condition subsiding in most cases in 2-6 months; however, recurrence and prolonged duration have been reported. Ten percent of patients exhibit progressive visual loss, and there is about a 5% mortality rate.

The syndrome is divided into two general categories—one in which the condition is apparently due to a major lateral sinus thrombosis following middle-ear infections or head injury, and one in which etiology is unknown but there may be an increased volume of cerebral spinal fluid, a hormone imbalance during pregnancy, or hypertensive encephalopathy. The second category embraces chiefly women who are of childbearing age and in whom there is often associated obesity, pregnancy, menstrual disorders, Addison's disease, steroid or other hormonal imbalance, or allergic states. Progressive visual failure tends to be more common in this group and to occur earlier than the degree of papilledema would suggest.

No cause was found in either of the cases described above. Since many cases occur between pregnancies, the pregnancy hormone imbalance theory is not always valid. Neither of our patients had generalized hypertension or a gross lesion. Cerebral venous thrombosis was not proven in either, and neither patient was obese. The disease also occurs in males and children, so that pregnancy per se cannot be the cause; it may be more readily recognized in pregnancy because of the additional care and observation given the pregnant woman.

It appears that the prognosis for mother and infant is good. In both the cases presented there had been a progressive increase in the size of the physiologic blind spot. Sterilization was requested and performed in both cases after progressive visual loss was noted.

Summary

Two cases of recurrent pseudotumor cerebri (benign intracranial hypertension) during pregnancy is presented in which sterilization was performed because of progressive visual loss. A brief discussion of the disease and etiologic theories is also presented.

COMPARISON OF HEMODYNAMIC RESPONSES TO WHOLE BLOOD AND PLASMA EXPANDERS IN CLINICAL TRAUMATIC SHOCK

Joseph S. Carey MD, Robert S. Brown MD, Neil W. Woodward MD, See Tao Yao MD, and William C. Shoemaker MD, Chicago, Illinois.

Surgery, Gynecology & Obstetrics 121(5): 1059–1065, November 1965.

Blood, as the natural intravascular fluid, has been considered the ideal replacement therapy for hemorrhagic and traumatic shock. The hemodynamic consequences of blood transfusions, however, have not been extensively investigated. Blood is a complex multiphasic suspension of cellular elements, large molecular and colloidal particles, an emulsion of fats, and a solution of crystalloids and electrolytes. Because of these factors, blood exhibits peculiar flow properties in the microcirculation. The viscosity of blood has been studied in relation to its velocity by Wells and Merrill. Dintenfass has related changes in viscosity to reversible internal structural alterations of the blood. That these properties may assume pathologic significance has been appreciated only recently.

From the Department of Surgical Research, Division of Surgery, Hektoen Institute for Medical Research, Cook County Hospital, Chicago.

The flow properties of blood in low perfusion systems may not be ideal. The addition of salt or colloidal solutions in experimental hemorrhagic shock not responding to reinfusion of shed blood resulted in improved survival as shown by Carrico and his associates and by McPherson and Haller. Further, in extracorporeal circulation, DeWall and Long and their associates have shown that salt and colloidal solutions are superior to blood alone as a priming solution. The improvement in perfusion seen with hemodilution suggests that the presence of erythrocytes in the priming or infusion solution may produce detrimental effects with low flow rates during perfusion states.

Studies of the microcirculation by Gelin related injury and burns to increased blood viscosity and intravascular aggregation of erythrocytes. These pathologic changes, which are related to the compo-

sition of blood, may be reversed by lowering the concentration of red cells or by changing the colloidal nature of the plasma.

Previous studies from this laboratory demonstrated marked improvements in circulation after low viscosity dextran administration to shock patients. The improvements in flow were proportional to the severity of circulatory failure present.

The present report is a comparative evaluation of hemodynamic responses of a series of patients to infusions of whole blood and various plasma expanders. These comparisons were made on postoperative patients who were in, or had recently recovered from, a state of shock incident to surgical trauma and hemorrhage.

Methods and Materials

Twenty postoperative patients from the Surgical Services of the Cook County Hospital were studied. All had undergone major abdominal surgery associated with varying degrees of blood loss in the previous 48 hours. All but 2 had manifested an acute episode of shock as judged by clinical evaluation of vital signs; 9 were in a state of shock at the time of the study.

The patients received infusions of whole blood, plasma, low viscosity dextran, clinical dextran, albumin, and saline. For purposes of comparison, 500 milliliters of each agent were given, in random order, over a period of 1 hour. The order of the infusions was dictated somewhat by the needs of the patient. All but 4 patients received low viscosity dextran and at least one other agent. In many, there was a return to baseline values several hours after infusion. However, it was found frequently that the low viscosity dextran administration produced a marked and lasting response after which the previous low baseline values were not reached.

A needle was inserted into the femoral artery for pressure monitoring and blood sampling. A polyethylene catheter was introduced into the superior vena cava through the brachial vein or the subclavian vein for monitoring central venous pressure and injection of dye. Pressures were recorded on a dynograph through strain gauge transducers using a saline-filled catheter system.

Cardiac output was determined by the Steward-Hamilton method using indocyanine green as the indicator. The measuring system included a constant withdrawal pump, a cuvette densitometer, and an instrument recorder. The recording system was sterilized and blood was reinfused after each dye injection so as not to limit the number of cardiac output determinations.

Mean transit time was estimated from the cardiac output curves with allowance for lag in the recording system. Initially, these transit times were calculated by the summation method to determine the exact time that half the dye traversed the heart and lungs. However, it was found that simply estimating the transit time from the shape was sufficient, providing the shape of the curves was similar throughout the study. This simpler and more expeditious method was compared with the standard method in a series of curves; there was general agreement of the two methods. Since the transit time is dependent on the placement of the catheters, especially the central venous catheter, the absolute values are not as important as the changes noted during the course of each study. Since the same method of estimation of transit time was used on each curve, significantly large and reproducible changes were thought to be valid. The central blood volume was calculated by multiplying mean transit time by the cardiac output; this value, therefore, is subject to the same errors and interpretations as the transit time. Total peripheral resistance was calculated using the following formula:

$$TPR = \frac{\text{Mean arterial pressure-central venous pressure} \times 7992}{\text{Cardiac output}}$$

Several control measurements were made before infusion of each agent. Sequential measurements were made during the time of infusion and for several hours thereafter.

The following blood volume expanders were studied: (a) compatible whole blood; (b) low viscosity dextran of mean molecular weight 40,000 in physiologic saline; (c) clinical dextran of mean molecular weight 80,000; (d) plasma; (e) 25 grams of albumin diluted into 500 milliliters of saline; and (f) physiologic saline. A 1 hour infusion of 500 milliliters of each of these agents was administered in randomized order. Hemodynamic measurements were made before, during and after administration of each agent.

Results

Figure 1 illustrates a representative study on a 67 year old Negro male, who underwent a gastric resection for a massively bleeding gastric ulcer, 24 hours before the study. He was in a state of shock throughout the operation and during most of the study. He received low viscosity dextran albumin, and whole blood over a 16 hour period. During this time he also received maintenance fluids, as well as other routine care. Responses to the agents were

typical of the general results and were particularly significant in this patient, as baseline values were essentially the same before infusion of each agent. Infusion of low viscosity dextran was marked by increased cardiac output, decreased mean transit time, rise in central venous pressure, slightly increased arterial pressure, and minimal changes in pulse rate; peripheral resistance decreased markedly and both central blood volume and stroke volume increased. The responses to albumin infusion were similar but less marked. There was little or no hemodynamic change in response to whole blood infusion.

Although improvements in circulation were seen in shock patients receiving whole blood, these responses were much less than the response to low viscosity dextran administration. Whole blood infusion in the compensated group resulted in a slight drop in cardiac output, increased transit time, and increased total peripheral resistance. Infusion of low viscosity dextran produced significant improvements in all parameters in both groups. The data from 9

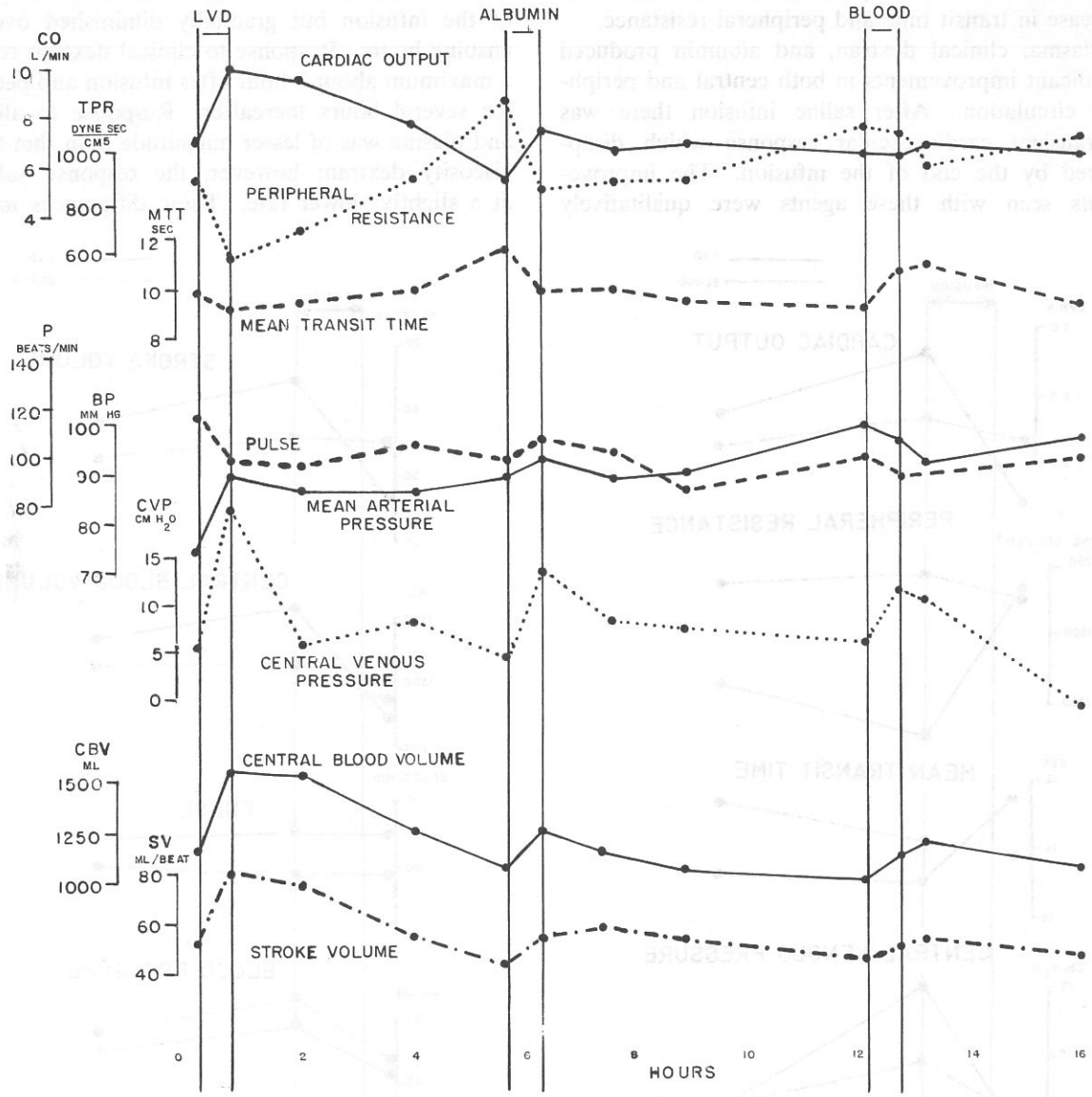

Fig. 1. Data from a representative study illustrating circulatory responses to low viscosity dextran, albumin, and blood. Five hundred milliliters of each agent were given over a 1 hour period. Measurements were made before, during, and at intervals for several hours after administration of each agent. This study demonstrates marked changes after low viscosity dextran, lesser changes with albumin, and little or no change with whole blood.

patients who received both agents are illustrated in Figures 2 and 3. In this comparative study cardiac output increased markedly after low viscosity dextran but only slightly after blood administration. Shift of blood to the central circulation, indicated by the marked increase in central venous pressure, central blood volume, and stroke volume was seen after low viscosity dextran, only minimal changes after whole blood administration. Low viscosity dextran produced a marked drop in total peripheral resistance and decrease in transit times, which indicated improved flow rates. By contrast, blood caused an increase in transit time and peripheral resistance.

Plasma, clinical dextran, and albumin produced significant improvements in both central and peripheral circulation. After saline infusion there was a transient cardiovascular response which disappeared by the end of the infusion. The improvements seen with these agents were qualitatively similar to those of low viscosity dextran. From a quantitative point of view, the responses of low viscosity dextran were compared with the response of each of the other agents using each patient as his own control. These data indicate that the responses to low viscosity dextran are generally greater than the responses to the other plasma volume expanders.

Comparisons of the time course of cardiac output responses to the different plasma volume expanders are illustrated in Figure 4. There was an early transitory response to saline infusion. Peak response to low viscosity dextran occurred at about the end of the infusion but gradually diminished over the ensuing hours. Response to clinical dextran reached a maximum about 1 hour after infusion and persisted for several hours thereafter. Response to albumin and plasma was of lesser magnitude than that to low viscosity dextran; however, the response subsided at a slightly slower rate. These differences may be

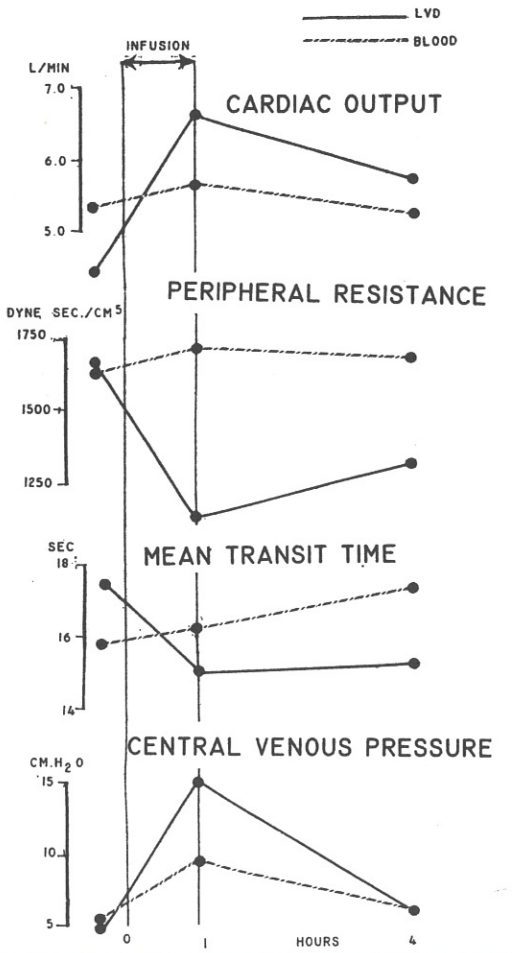

Fig. 2. Comparisons of the cardiac output, peripheral resistance, mean transit time, and central venous pressure responses of 9 patients who received both low viscosity dextran and whole blood.

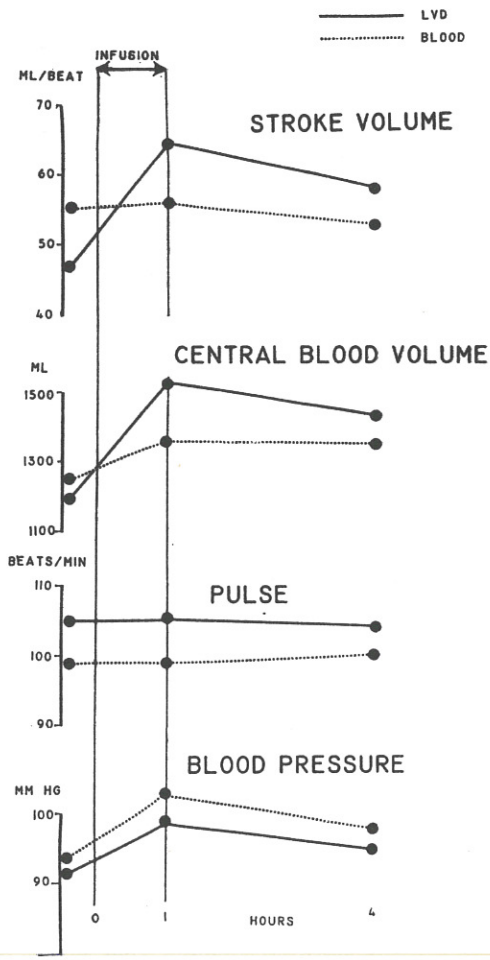

Fig. 3. Comparison of the stroke volume, central blood volume, pulse, and blood pressure responses of 9 patients who received both low viscosity dextran and whole blood.

related to the size, shape, and electrical charge of the colloidal particles as well as the rheologic properties of these agents.

Discussion

The present study demonstrates considerable difference in the hemodynamic responses of shock patients to infusion of whole blood as compared with plasma volume expanders. Increased central venous pressure and central blood volume in the face of increased cardiac output and stroke volume occurred after infusion of low viscosity dextran and other plasma volume expanders but not after infusion of blood. This observation suggests that low viscosity dextran and other plasma expanders shift blood to the central circulation. Decreased peripheral resistance and transit times were seen after low viscosity dextran but not after blood transfusions; this finding also suggested improved circulatory flow. Hypovolemic shock patients will respond favorably to blood transfusions. However, these data indicate that whole blood transfusions are less effective in improving cardiovascular function than plasma volume expanders in patients who have had adequate blood replacement but who are still in a state of shock.

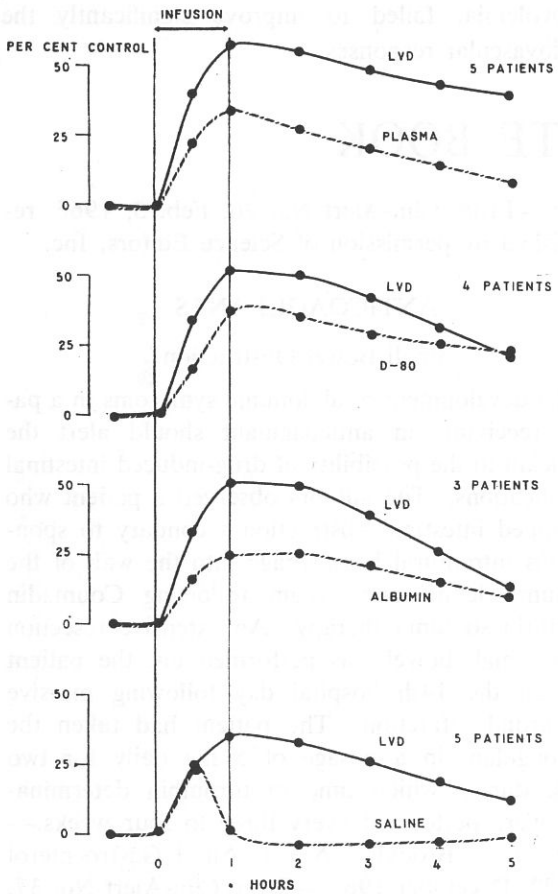

Fig. 4. Comparison of the magnitude and time course of the cardiac output response to infusion of low viscosity dextran, plasma, clinical dextran (D-80), albumin, and saline. Paired comparisons were made between low viscosity dextran responses and each of the other agents administered to the same patient.

It would appear that the degree of cardiac response is related to the presence of erythrocytes in the infusion. Intravascular cellular aggregation in the hepatic and peripheral microcirculation may limit the venous return to the right side of the heart and the volume of blood in the central circulation.

The administration of whole blood may increase cellular aggregation and, thus, may account for the ineffectiveness of whole blood as a replacement solution in normovolemic hemorrhagic shock. Obviously, a certain minimum concentration of erythrocytes is necessary for proper oxygen transport, but patients with chronic anemia frequently tolerate extremely low hematocrit levels without endangering life. Roe and his associates among others have used effectively hemodilution resulting in hematocrit values of 20 to 25 percent in open heart procedures.

Numerous studies have demonstrated that the viscosity of blood is determined to a large extent by the concentration of the large molecular particles as well as the concentration of erythrocytes. Similarly, erythrocyte aggregation has been related to the balance of large molecular particles in the plasma. Thus, the superior hemodynamic effects of low viscosity dextran may be accounted for by an alteration in this balance; the presence of smaller particles decreases the tendency toward erythrocyte aggregation.

The net effect is a reduction in viscosity and improvement in flow properties of the blood. However, these advantages are limited by the relatively rapid excretion of low viscosity dextran by the kidney. Continuous infusion of 2 to 3 grams of low viscosity dextran per kilogram of body weight per day may be required for maximum effectiveness.

The need for reassessment of blood volume therapy after trauma and hemorrhage is suggested by this study. The data indicate that greater cardiovascular improvement follows the administration of low viscosity dextran and other plasma expanders as compared with blood transfusions. For this reason plasma volume expanders may be preferable as replacement solutions when the hematocrit value is above 25 or 30 percent.

Summary

The hemodynamic responses of whole blood, low viscosity dextran, clinical dextran, plasma, albumin, and saline were evaluated in a series of 20 postoperative patients. Nine patients were in a state of shock at the time of the study; the remainder were partly resuscitated with transfusion therapy but were considered to be in compensated shock. Serial measurements of cardiac output, mean transit time, arterial and central venous pressures, total peripheral resistance, central blood volume, and stroke volume were determined before, during, and after the administration of each of the various types of plasma volume expanders.

A marked and significant hemodynamic improvement followed the administration of low viscosity dextran in both groups of shock patients. These effects were minimal or absent after blood transfusions. Infusions of 500 milliliters of normal saline produced rather transient hemodynamic effects which often were over by the end of the infusion. When compared to similar infusions of low viscosity dextran in the same patient, clinical dextran produced a lesser but more lasting hemodynamic improvement. The responses to albumin and plasma were of similar time course but were only about 50 percent of the response to low viscosity dextran.

The markedly different cardiovascular responses to blood and plasma volume expanders suggests the need for reassessment of blood volume replacement in the therapy of shock. Plasma volume expanders lowered the hematocrit value and decreased peripheral resistance and transit time.

Low viscosity dextran reduced blood and plasma viscosity and improved flow properties of blood in small vessels. The net effect was increased venous return and shift of blood volume to the central circulation. By contrast, blood transfusion increased erythrocyte concentration, viscosity, and, except in hypovolemia, failed to improve significantly the cardiovascular responses.

FROM THE NOTE BOOK

GOLF BALLS

Liquid Centers

The cores of liquid center golf balls are under high compression (2,000 to 2,500 pounds per sq in). Penetration of the core releases the liquid in an explosive manner with possible ocular damage. The composition of the liquid centers varies, but some of the major ingredients include water, gelatin, corn syrup, and silicone. At least one American manufacturer uses barium sulfate in the liquid center.—Penner, (Washington, D.C.), Arch Ophthalmol 25: 68, January 1966.—From Clin-Alert No. 25, Feb. 3, 1966, republished by permission of Science Editors, Inc.

AORTOGRAPHY

Embolic occlusion of a renal artery occurred in a 69-year-old patient subjected to abdominal aortography. A radiopaque Teflon catheter with an end-occluding obturator was used. The presence of the obturator probably facilitated clot formation. To minimize clot formation such catheters should be flushed more frequently and more forcefully than catheters without an obturator.—Morrow & Amplatz (Minneapolis, Minn.), Radiol 86:57, January 1966.—From Clin-Alert No. 26, Feb. 3, 1966, republished by permission of Science Editors, Inc.

ANTICOAGULANTS

Small Bowel Obstruction

The development of abdominal symptoms in a patient receiving an anticoagulant should alert the physician to the possibility of drug-induced intestinal complications. The authors observed a patient who developed intestinal obstruction secondary to spontaneous intramural hemorrhage into the wall of the jejunum, ileum, and cecum following Coumadin (warfarin sodium) therapy. An extensive resection of the small bowel was performed but the patient died on the 14th hospital day following massive myocardial infarction. The patient had taken the anticoagulant in a dosage of 5 mg daily for two years, during which time prothrombin determinations were performed every three to four weeks.—Yvars et al (Brooklyn, N.Y.), Am J Gastroenterol 44:572, December 1965.—From Clin-Alert No. 37, Feb. 3, 1966, republished by permission of Science Editors, Inc.

BLOOD DONATIONS

Americans have donated more than 38,000 units of whole blood to support U.S. armed forces in

Vietnam. Majority of donations—well over 30,000 units—have come from students in 145 colleges and universities. Colleges contributing more than 1,000 units include: Univ of Illinois; Mississippi State Univ.; Univ of Alabama; and Auburn Univ. Red Cross is handling the special blood collections at request of DOD.—Commanders Digest 2(14):2, Feb. 16, 1966.

CHLORAMPHENICOL

Suppression of Antibody Formation: It has recently been established that chloramphenicol (Chloromycetin) can modify both primary and secondary immune responses (Clin-Alert No. 334, 1964; Clin-Alert No. 252, 1965). The present authors demonstrated the ability of chloramphenicol to suppress or modify experimentally induced immune nephritis presumably by impairment of antibody synthesis. It is suggested that chloramphenicol suppresses antibody formation during the inductive phase by interfering with the deposition of newly formed m-RNA on ribosomes.—Weisberger et al (Cleveland, Ohio), J Lab & Clin Med 67:58, January 1966.

Hematopoietic Depression: Twenty-two patients with chronic renal or hepatic disease were given 3 Gm chloramphenicol (Chloromycetin) or tetracycline daily for 21 days. Tetracycline did not produce significant hematopoietic changes. Chloramphenicol however, induced reversible erythroid depression in 5 of 10 patients. The hematopoietic changes included reticulocytopenia and an average fall in hemoglobin of 2.7 Gm/100 ml, a rise in serum iron, cytoplasmic vacuolation of early erythroid forms and granulocytic precursors, and normoblastopenia with a shift to earlier red cell precursors. In patients with renal disease, the susceptibility to chloramphenicol-induced blood changes was not related to the degree of renal insufficiency present.—Gussoff & Lee (Brooklyn, N.Y.) Am J Med Sci 251:8, January 1966.—From Clin-Alert No. 40, Feb. 18, 1966, republished by permission of Science Editors, Inc.

SPARTINE SULFATE

Potent, Capricious Oxytocic

"Medical history repeats itself. Once again the physician's desire for a safe but effective pharmaceutical has led to the widespread use and abuse of a new drug. This time it is spartine sulfate." The authors employed the oxytocic drug intramuscularly for induction or stimulation of labor in 322 patients. Tetanic uterine contractions occurred in four mothers with one fetal death. There were four cases of placental abruptions with one fetal death. Abnormally rapid labor ensued in one-third of patients and was the cause of many instances of fetal distress. The onset of action of spartine sulfate is quite variable (a few minutes to hours). The ultimate success or failure of treatment cannot be predicted by the patient's response to the first injection.—Newton et al (Honolulu, Hawaii), Am J Obst & Gynec 94:234, January 15, 1966. [For additional information see Clin-Alert No. 172 & 233, 1963; Clin-Alert No. 67, 1964.]—From Clin-Alert No. 44, Feb. 18, 1966, republished by permission of Science Editors, Inc.

LIBRAX

Withdrawal

Approval of the new drug application applying to Librax Capsules (clidinium bromide + chlordiazepoxide), Hoffman-LaRoche, Inc., was withdrawn by F.D.A. effective January 19, 1966. This action was taken after clinical evidence showed that use of Librax Capsules is associated with the occurrence of accentuated anticholinergic effects. In addition, the product was found to contain impurities which may or may not cause serious side effects.—Federal Register 13:1015, January 26, 1966.—From Clin-Alert No. 45, Feb. 18, 1966, republished by permission of Science Editors, Inc.

MYLERAN

Pulmonary Interstitial Fibrosis

Myleran (busulfan) is widely employed in treatment of chronic granulocytic leukemia. The toxicity of Myleran is low; the only serious effect noted has been bone marrow depression, and even this is very unusual if the dosage is kept within prescribed limits. However, the present authors observed two patients who developed diffuse pulmonary interstitial fibrosis while on Myleran. The condition is an unusual result of therapy but its effects are so devastating that all who use Myleran should be aware of the reaction. It is possible that irreversible damage may be avoided by early cessation of Myleran therapy.—Smalley & Wall (Columbus, Ohio), Ann Int Med 64:154, January 1966.—From Clin-Alert No. 47, Feb. 18, 1966, republished by permission of Science Editors, Inc.

MEETING OF SOCIETY OF MILITARY OTOLARYNGOLOGISTS

The Society of Military Otolaryngologists, LCOL Frederick Collins, USAF, President, held its 14th annual meeting at the 5th Army Officers Mess, Chicago, Illinois, 20 November 1965. Dr. Paul Holinger, the honored guest and his wife attended. A plaque was presented to Dr. Holinger honoring him for his service to military otolaryngology. During the regular business meeting, plans were formulated to the Society to publish a bulletin twice a year. The next meeting will be held on October 20, 1966 at the same place.—From material submitted by CDR George P. Hart MC USN, Secretary.

SELECTIVE SERVICE SYSTEM TO PROVIDE MALE NURSES

Department of Defense has asked Selective Service System to provide 900 male nurses for active duty in Army and Navy, beginning this April. This is first call placed with Selective Service for nurses since President Johnson signed authorizing Executive Order Jan. 18, 1966. It is anticipated that male nurses will serve in commissioned or warrant officer grades.—Commanders Digest 2(17):2, February 26, 1966.

LUNG CANCER IN WOMEN

Scientists at the National Cancer Institute, National Institutes of Health have confirmed an earlier finding that, among patients operated on for lung cancer, women live longer than men. In their study of 504 women and 511 men, the Public Health Service statisticians also identified several factors that help to explain this sex difference in survival rates: the type of tumor, extent of disease, and amount of surgery performed.

A marked difference was found between male and female patients in respect to tumor type, with adenocarcinomas and alveolar cell tumors occurring about 3 times more frequently in women than in men. Among patients with these types of tumors, survival rates were substantially higher for women, while among patients with epidermoid carcinoma—the most common type of lung cancer in men—survival rates in men and women were about the same. Among both men and women with adenocarcinomas or alveolar cell tumors, 3 of every 4 had growths confined to one lobe; while among patients with epidermoid carcinomas, women were more likely than men to have a tumor of limited extent.

The more frequent occurrence of adenocarcinomas and alveolar cell tumors in women, and the more frequent occurrence of tumors limited to one lobe account for the fact that, among surgically treated patients, almost one-half of the women, compared to one-fourth of the men, had only part of the lung removed (a lobectomy). However, among all patients with localized disease treated by lobectomy, the outlook remained substantially more favorable for women than men. Thus, part of the survival advantage in favor of women remains unexplained by the present study which was reported in the February issue of the Journal of the National Cancer Institute by Roger R. Connelly, Dr. Sidney J. Cutler, and Paula Baylis of the Institute's Biometry Branch.—USDHEW, PHS, February 28, 1966.

DENTAL SECTION

DENTISTRY'S RESPONSIBILITY IN THE ATTAINMENT OF OPTIMUM HEALTH

Durocher, R. T., Jour Am Col Den 33(1): 34–42, January 1966.

Dentistry is on the threshold of a golden era. Whether dentistry will step beyond the threshold will depend on whether the leaders of the profession will make the courageous effort of introspection. Such a self-examination must be analytical to the point of self-criticism. Is the purpose of our existence to preserve the dentition? The author proposes that our mission is far more fundamental: the underlying essence of our responsibility is the attainment of optimum well-being—the fulfillment of man. What can dentists contribute to optimum well-being? At the top of the suggested list of services is prevention. Historically, prevention has generally meant patient instruction, prophylaxis, and extension for prevention in cavity preparation. More recently, the concept of prevention has included mouth guards, use of fluorides, and interceptive orthodontics. In the near future, prevention will extend to "well-patient" programs.

The role of the dentist as a diagnostic consultant

continues to grow. On the relationships of oral and systemic diseases, much has been learned in recent years. In this advancing knowledge, not only the researcher, but the practicing dentist must expand the attitude of inquiry relative to each patient's oral health. Through inquisitiveness, and the development of new techniques, such as cephalometry, laminography and cinefluoroscopy, improvement in diagnostic acumen will lead to more accurate treatment. Accepting our role in the fulfillment of man, dentistry will find ways to bring dental care to the country dweller, the handicapped, the chronically ill. Dentistry will learn to consult freely with the psychiatrist and the social worker; to solicit unabashedly the advice of our fellow general practitioners as well as specialists. Dentists will be motivated to cooperate with physicians in facing special medical problems, such as civil disasters; to contribute to social action for meeting health needs of the total population. The time is appropriate for the profession to formulate concepts and to devise educational programs which will prepare the dentist to adapt to any reorganization which may arise among the health professions of the future.

DIETARY FLUORIDES AND CARIES PREVENTION

Schlesinger, Edward R., New York State Department of Health, Albany, N.Y., Am Jour Pub Hlth 55(8): 1123–1129, August 1965.

Theoretically there is no reason why fluoride prescribed in tablet, lozenge or liquid form in proper dosage should not be as effective for individual children as fluoridated water at the optimal concentration. One of the problems is the uncertainty of translating literally to individual use the experience gained from water fluoridation.

At fluoride levels used in water fluoridation, the maximum number of persons receive the desired dental benefits without danger of systemic effects to any individuals in the community. Water fluoridation reduces the prevalence of malocclusion as well as of dental caries, and reduces the cost of dental care for children.

The administration of dietary fluoride in pregnant women for control of dental caries in children cannot be justified at the present time on the basis of available evidence.

Children drink varying amounts of fluids and varying proportions of tap water in total fluid. Walker and his co-workers found that breast-fed infants, for example drank on the average of only 19 ml of tap water daily in contrast to about 300 ml in bottle-fed infants. The consumption of milk in older children is far more variable than that of water. Apart from the excessive cost of adding fluoride to milk the administrative difficulties all but preclude serious consideration for this medium. This hardly forms a solid basis for individual dosage of fluorides although, Arnold, McClure, and White found that a group of properly motivated professional families could obtain benefits from individual dosage of fluoride in tablets or liquids for individual children who are denied the benefits of fluoridation. Community programs for the administration of fluoride to individual children as substitute for fluoridation have been beset by difficulties. Apart from greatly increased cost and personnel time needed, these programs have not met with enough community interest and cooperation, especially among population groups with the greatest need for dental care to justify their continuance.

The administration of fluoride—vitamin combinations to children is not justified by any scientific estimate. The use of inflexible combinations of nutrients makes it all but impossible to adjust the fluoride intake to the need of the individual in relation to the fluoride level in the community water supply.

Editor's note: This article's conclusions are consistent with a previous one (U.S. Navy Medical News Letter 45(9): 17, May 14, 1965), which concluded that the dental officer should take the position that substitution of dietary fluorides for fluoridation of station water supply (BUMEDINST 113310.1A) is justified only when some engineering feature precludes fluoridation of the station water.

FLUORIDE PROTECTION OF BONES AND TEETH

Sognnaes, R. F., Science 150(3699):989–993, November 19, 1965.

The potential benefits of ingested fluoride in the management of various general illnesses, notably metabolic bone diseases, has generated new interest in the extent to which tissue tolerates fluoride ion. Since tissue culture tolerates 5–10 PPM fluoride ion, and since recent medical applications use 20–100 mg of fluoride ion per day, it is readily apparent that consumption of water containing 1 PPM fluoride ion (total 0.5–1 mg per day) for caries prevention provides a higher margin of safety than is generally

understood. The purpose of this article is to provide a summary of recent new information concerning uses of fluoride in both medicine and dentistry, and secondarily to illustrate the baselessness of continuing concern over the presumed "poisoning effects" of fluoride supplemented drinking water.

In tissue culture, cellular reproductivity continues in the presence of fluoride ion greater than can be reached in the body's tissue fluids from oral ingestion. Fluoride concentrations up to 20 PPM in organ cultures of young rat bone had no demonstrable effect on DNA formation and protein synthesis.

One of the remarkable aspects of fluoride ingestion and metabolism is the fact that it is almost impossible to raise markedly the blood plasma fluoride level by oral ingestion of fluoride at extremely high concentration. Long term consumption of water containing double the recommended 1 PPM fluoride had no demonstrable effect on human plasma fluoride levels. Renal clearance of ingested fluoride is highly efficient; in man, only 10% of an oral dose is retained in the plasma one hour later.

Twenty years ago 30 PPM fluoride was used in an effort to protect the skeleton of patients with idiopathic osteoporosis. Fluoride doses of 80 to 400 mg a day for four to six months have been prescribed for various illnesses, mostly cancer; and this extraordinarily high dosage produced no observable toxicity. More recently people with disturbances in calcium metabolism and destructive skeletal diseases, e.g. postmenopausal bone defects, osteoporosis, Paget's disease, osteogenesis imperfecta, multiple myeloma and metastatic carcinoma spreading into bone, have been treated with fluoride. Toxic effects have not been observed. These uses suggest that fluoride ion has a general effect on bone, not specific interference with a metabolic abnormality. Included with this general effect of fluoride on bone is increased calcium retention and resultant increasing density. Current activity in fluoride therapy of bone diseases suggests that its effect on alveolar destruction merits investigation. Similarly, local injection of higher concentrations of fluoride ion may have a hitherto unknown preventive benefit on developing teeth. Better protection and stabilization of human calcified tissues than has been achieved to date may well become attainable through further studies on optimum timing, dosage and duration of treatment with fluorides.

PERSONNEL AND PROFESSIONAL NOTES

FLEET ORAL HYGIENE UNIT OPENED. RADM F. M. Kyes DC USN, Assistant Chief of the Bureau of Medicine and Surgery (Dentistry) and Chief, Dental Division, was awarded the Rhode Island State Dental Society's Medal of Award at the Annual Meeting held in Providence, Rhode Island, January 25–26, 1966.

While in the area, RADM Kyes attended the Ribbon Cutting Ceremony at the U.S. Naval Station, Newport, Rhode Island. The Ceremony was held in conjunction with the opening of the new Fleet Oral Hygiene Unit No. 1, located at Pier No. 2 of the Naval Station. The purpose of the Oral Hygiene Unit is to bring the examination and preventive dentistry treatment to the patient. Being located on the dock means a savings of approximately 750 hours per year per destroyer; and for 60 destroyers, this means 45,000 man hours. The preventive treatment will eliminate one cavity per man per year, thus eliminating another trip to the dental clinic. This doubles the 45,000 man hours, making 90,000. The restoration of each cavity which would have occurred without the treatment would take an hour of a dental officer's and dental technician's time. This would be another 15,000 man hours. Accordingly, it is expected that the Oral Hygiene Unit will account for the savings of 110,000 man hours per year.

DENTAL OFFICER PRESENTATIONS. The U.S. Naval Academy Dental Department, Annapolis, Maryland, hosted a meeting of approximately fifty members of the Maryland Western Shore Dental Society on 27 January 1966 at the Naval Academy Officer's Club. In addition to those table clinics presented by the civilian members of the Society, the following table clinics were presented by dental officers on duty at the Naval Academy.

"Anatomical Consideration in Pulp Access and Pin Re-enforcement"—CDR W. B. Gregory DC USN and LT J. B. Holcomb DC USN.

"Simplified Single Crown Technique"—CDR Andrew Wyda DC USN.

"Technique for Palatal Odontectomy"—CDR Charles S. Scruggs DC USN.

"A Simplified Porcelain Dowel Crown Technique"—LCDR William J. Watson DC USN.

CAPT William R. Stanmeyer DC USN is Senior Dental Officer at the Naval Academy, and Doctor

Alan Harquail is President of the Maryland Western Shore Dental Society. This professional meeting with both civilian and military groups participating is becoming an annual event for the Dental Society.

CAPT C. H. Prince, Jr. DC USN and LCDR E. T. Witte DC USN presented lectures to the student flight surgeons at the U.S. Naval Aerospace Medical Institute, Pensacola, Florida, on 10–11 February 1966. CAPT Prince's lecture was entitled "Traumatic Injuries Involving the Maxilla and Mandible", and LCDR Witte lectured on "Body Identification and Infections of Dental Origin."

LCDR R. W. Longton DC USN, Assistant Dental Research Officer, Dental Research Facility Division, Dental Department, U.S. Naval Training Center, Great Lakes, Illinois, participated in a seminar on "Dental Office Asepsia" before the Northwestern University Dental School Staff. The meeting was held on 10 February 1966 at Northwestern University, Dental School, Chicago, Illinois.

CDR R. W. Didion DC USN, Marine Corps Recruit Depot, San Diego, California, presented a lecture to the Future Teachers Association of the Point Loma High School, San Diego, California entitled "Comparison Between Education in Russia and the United States—Past and Present", in January 1966.

DENTAL OFFICER APPOINTMENT. LCDR W. R. Cotton DC USN, Dental Research Department, Naval Medical Research Institute, Bethesda, Maryland, has accepted an appointment by the Editor of the American Dental Association to abstract articles for Oral Research Abstracts. LCDR Cotton will be abstracting articles in the field of microanatomy.

NAVAL DENTAL SCHOOL REQUESTS COPIES OF A BOOK. To support the Extension Education Program, the Naval Dental School has need for additional copies of Irving Glickman's text book entitled, "Clinical Periodontology," 2nd Edition, 1958, Saunders. It is pointed out that the 3rd Edition, 1964 is now available and will be recommended in a forthcoming change to BUMED INST 6820.4G. If any person or activity has a copy of the 2nd Edition, which he would donate to the School, please forward it to the Commanding Officer, U.S. Naval Dental School, National Naval Medical Center, Bethesda, Maryland 20014.

ADVANCE NOTICES OF REASSIGNMENTS TEMPORARILY DISCONTINUED. Due to a large volume of correspondence, and an increase in the normal workload, it is necessary that advance notices of reassignments be temporarily discontinued. Occasionally, when very senior billets are involved, or where lead time is shorter than usual, the individual concerned will be notified by letter or telephone. It is hoped the "flimsy letter" can be made a routine procedure again in the near future.

CASUALTY CARE TRAINING PAYS OFF. During the arrival of Vietnamese officials at Honolulu Airport, a U.S. Marine Corps honor guardsman collapsed, and was carried to a baggage counter. LCDR Harris J. Keene DC USN, stepped forward, prepared to assist in his care. Doctor Keene noted a sudden loss of vital signs. He instituted mouth to mouth resuscitation. Subsequently, he performed closed chest cardiac massage, while an unidentified person assisted with mouth to mouth resuscitation. When the marine's pulse and respiration were restored, he was taken by ambulance to Tripler General Hospital. Upon subsequent inquiry, Doctor Keene was informed that a diagnosis of Hypoglycemia had been established and that the marine was released from the hospital after treatment. This life saving example illustrates the value of the U.S. Naval Dental Corps continuing program of training in casualty care procedures.

After a tour of duty at the Dental Research Facility, U.S. Naval Training Center, Great Lakes, Illinois, LCDR Keene was attached to 1st Marine Brigade, Detachment 1, 5th Dental Company, MCAS Kaneohe, in September 1965.

OCCUPATIONAL MEDICINE SECTION

HEALTH HAZARDS ASSOCIATED WITH POLYURETHANE FOAMS

Carl U. Dernehl MD, New York, N.Y., JOM 8(2):59–61, February 1966.

The diisocyanates, while known as chemical entities for many years, have only relatively recently become significant factors in industry. They are being used more widely each year: among their applications are adhesives, lacquers, and primarily foamed products commonly identified as polyurethane foams.

Until recently, most polyurethane foam operations were performed in factories under relatively controlled conditions. Lately, the use of foamed-in-

place polyurethanes has invaded the construction industry, where workmen are not renowned for the care with which they handle materials.

Because of the wide use of foamed products, attention will be devoted to problems related to foamed polyurethanes. While the final cured foam is an inert product, the unreacted ingredients of a foam may be troublesome. The earliest foams were relatively simple formulations, but efforts to tailor the foam for specific properties and to improve its quality have led to the introduction of a large number of ingredients, any of which may be constituents of a single foam formulation. Basically, however, the foams still consist of a diisocyanate, a polyol, a catalyst, a blowing agent, and frequently a catalyst accelerator. Of these ingredients, only the polyol is of little concern. The others may have varying degrees of harmful effects.

The most troublesome ingredient is the diisocyanate. Toluene diisocyanate (TDI) has been used perhaps more than any other isocyanate. Its toxicity has been reported by Zapp who notes that the acute toxicity as measured by mortality is not great, but that TDI is irritating to the skin, eyes, and respiratory tract. Others have observed difficult breathing and what was called asthmatoid respiration in animals exposed to TDI vapors, but animals are notoriously difficult subjects in which to demonstrate an asthmatic state. Human experience has left no doubt of the ability of TDI to cause asthmatic breathing or asthma. The symptoms of persons exposed to TDI vary with the amount of exposure and depend also upon the degree of sensitization that may have occurred. Williamson reports on a series of cases in which contamination of the workroom atmosphere was generally significantly less than the threshold limit value of 0.02 ppm and only occasionally may have approached or briefly exceeded this level. The predominant symptoms in these persons were chest discomfort and breathlessness which were not immediately disabling and did not result in requests for medical attention. When medical care was requested, physical signs were rales, rhonchi, and decreased 1-sec. forced expiratory volume. Some persons ultimately developed disabling illness following continued exposure. All returned to normal following removal from exposure to TDI.

In contrast to this gradual onset of illness is our own experience in the manufacture of TDI. In this instance, individuals were exposed to temporary high vapor concentrations during operating difficulties or during repair work on equipment removed from the production unit. Reactions in some cases occurred upon the first known exposure to TDI. Within a few minutes of the exposure there was onset of tracheal and laryngeal irritation causing acute discomfort and severe coughing spasms which, if allowed to persist, led to embarrassed respiration and cyanosis. Subsequently, some individuals developed asthmatoid breathing as is seen with so-called asthmatic bronchitis. In the absence of specific therapy, the acute illness may cause several days of disability. In some workers, x-ray examination showed patchy areas of consolidation in the lung, and the patients were hospitalized by their family physicians with a diagnosis of pneumonia. Probably the condition represents a chemical pneumonitis. Similar findings have been reported. A certain number of workers who have suffered acute exposures will subsequently exhibit a sensitivity to TDI and will have true attacks of asthma following exposures from which their fellow workers will develop no symptoms. Still other individuals may never have any recognized symptoms of an acute exposure but will manifest evidence of sensitization on their first reported illness. It is probable that these persons become sensitized by repeated subclinical exposures, after which a minor exposure is sufficient to cause an attack of asthma. In our experience, it is also possible to develop sensitization of the skin. This has developed in workmen who were adequately protected by air-line respiratory equipment but who had repeated skin contact.

Many efforts have been made to control the TDI problem. One approach has been to select a diisocyanate of larger molecular size and a lower vapor pressure. Another has been the making of prepolymers which partially react the isocyanate radicals, the reaction of the remaining isocyanate being completed in the final foaming operation. These changes reduce the hazards of the process because they reduce the probability that high vapor concentrations will be formed. However, under sufficiently stressful conditions, sensitization may still be expected to occur, and the sensitized individual will still react to trace exposures with attacks of asthma. There is good reason to believe that cross-sensitization between diisocyanates exists and that probably the diisocyanate moiety is the active agent. However, sensitization to a diisocyanate does not indicate a sensitization to all isocyanates. For example, methyl isocyanate is a powerful sensitizer, but guinea pigs sensitized to TDI do not react to methyl isocyanate.

In some foams, certain aliphatic amines are used

as catalysts in the reaction. Among these are morpholine, methyl morpholine, ethyl morpholine, triethylene diamine, and tetramethyl butanediamine, to mention a few. While no clear-cut pattern of symptoms of general systemic effects has been noted which might be ascribed to exposure to these amines, local effects have been observed in some cases. Occasionally there have been reports of throat irritation which it is believed may be due to the amines. The absence of chest complaints and eye irritation suggests that TDI is not involved, although it certainly cannot be eliminated.

A characteristic lesion of the cornea of the eye has been observed in some workmen exposed to vapors of aliphatic amines. This lesion has been observed not only in men exposed to amines during the manufacture of polyurethane foam but also in some workmen during the manufacture of a large variety of amines. The usual experience is that late in the workday the affected employee becomes aware that he seems to be seeing everything through a bluish haze, and that point light sources are seen as having refractile rings around them. No symptoms of ocular discomfort are present in most of those affected. A few may have a vague sense of irritation.

The condition is self-limited and usually clears without any treatment within 3 or 4 hours after exposure ceases. Many instances are known in which the condition has occurred at the end of each workday for many days in sequence without demonstrable persistent harmful effect. Examination of the cornea shows a diffuse clouding to be present which, in extreme cases, may obscure the normal markings of the iris. Under slit-lamp microscopy, the cornea is seen to have a diffuse edema with many tiny vesicular collections of fluid within the corneal stroma. When this lesion appears, it must be accepted as evidence of exposure to excessive quantities of vapors of the amine catalysts and, as such, is undesirable even though present evidence suggests that no permanent or serious harmful effect occurs. Incomplete plant studies have shown that the lesion occurs when air concentrations of the substituted morpholines is 40 ppm or higher. The maximum air concentration at which no lesion appears is not known, but a threshold limit value of 20 ppm has been proposed for N-ethylmorpholine by the American Conference of Governmental Industrial Hygienists. Indirect hazards may be present because cases are known where individuals afflicted with the condition and driving home from work at night were blinded by the light of oncoming cars and were involved in serious accidents. In dim light, vision seems to be obscured very little. In bright light, there may be serious interference with vision.

In addition to the ability to cause a corneal edema, tetramethyl butanediamine has been noted to have a cycloplegic effect on the eye similar to that of atropine. Certain workmen using tetramethyl butanediamine reported prolonged blurring of vision which seemed to be different from the complaints associated with corneal edema. Examination at the start of the workday showed the cornea to be clear, but the pupil of the eye was widely dilated and failed to contract when exposed to light. No change occurred to accommodate for changes in visual focusing. Subsequently, it has been possible to demonstrate this effect in experimental animals, and Goldberg and Johnson have shown that the pupillary dilatation develops because of blocking of the ganglia of the parasympathetic nervous system which controls the circumferential constrictor muscle of the iris. This is not surprising in view of the known pharmacologic activity of a wide variety of amines. The precise concentration of vapors required to produce this effect is not known, but the presence of the condition must be considered undesirable even though other systemic effects have not been observed to occur.

In general, it seems to be true that the diisocyanates are rather completely reacted in the foaming process, particularly after a period of cure. We have tested cured foam on the skin of humans by the repeated-insult patch test without producing any reaction. The amines, however, may be present for considerable periods and are slowly released to the atmosphere. As a result, the curing rooms may have rather high concentrations of amine vapors even though the vapors of TDI may not be present in significant amount. When a slab of foam is cured and then cut and trimmed, there is little problem with vapors. When the foam is cut first and then cured, the cutting operation may present problems from both TDI and from amines.

Blowing agents may be added to foam formulations. While the foaming reaction develops carbon dioxide, which causes the foamed structure of the product, it is sometimes desirable to increase the amount of foaming which occurs. The foaming is often increased by adding a low-boiling-point fluorocarbon or chlorinated hydrocarbon such as methylene chloride. While the fluorocarbons are relatively nontoxic, the effects of the chlorinated hydrocarbons must be borne in mind.

The catalyst accelerators are commonly rather irritant materials and are frequently organic tin compounds. These are not new materials. They have a long history of use in the plastics industry where their ability to irritate and burn the skin and eye has been evident. Fortunately, in foams they are used in small amounts and probably contribute little hazard except at the time of their addition to the foam mix. During the foaming operation, their irritant properties are dwarfed by the irritant effects of TDI.

INDUSTRIAL HYGIENE: THE NEXT 25 YEARS

J. H. Sterner MD, Rochester, N.Y., National Safety News 91(2):30, February 1965.

Where is industrial hygiene headed in the next twenty-five years? Though it is difficult to estimate just how extensive the changes will be, I have predictions in five general areas where I foresee the greatest activity.

I should point out that not all are original with me; they have been synthesized from the clairvoyance of others and my own ideas.

Discipline Evolution

We have seen industrial hygiene evolve through a series of waves of discipline intermingling, born of necessity in meeting new and different problems. An ever-widening variety of new disciplines have been included so that the initial engineer/chemist/physicist/toxicologist/physician/industrial hygienist has been hybridized with such elements as the acoustical and audiological specialists, the meteorologist, the radiation biologist and health physicist, the epidemiologist, the ergonomicist, and a host of others.

I predict: Industrial hygiene will continue to wed with a greater variety of specialities, including—particularly as we move inevitably into areas involving the study of lower level and long-term effects, and the motivation of people—such categories as the population geneticist, the anthropologist, the psychiatrist and psychologist, the sociologist, the molecular biologist, and many others, some of which may not have as yet been differentiated.

In addition, industrial hygiene has moved outside of the plant and into the community. It is concerned with air pollution, pesticide intoxication, general population radiation, etc., so that it will be increasingly difficult to distinguish the boundaries of interest between industrial hygiene and other environmental health activities. This interfusion will continue and is certain to have a major influence on the identity and direction of industrial hygiene.

Industrial Hygiene Expansion

The limited availability of industrial hygiene service is a perennial topic with us. I don't believe it will have a single solution.

I predict: A continuing expansion of the employment of industrial hygienists at all levels of need, by an ever-larger number of industries. Congress will finally overcome its reluctance to "subsidize" occupational health and will recognize its responsibility to provide adequate governmental support to official agencies—national, state, and local, and for supporting a much broader scale of educational opportunities.

Small industry will be served by an increasing number of private consultants, and there will be a greater number of such specialists to meet reasonably small industry needs. At the same time, governmental agencies, particularly at the state and local levels, will expand their capability to one of preventive service as well as enforcement, and in many localities will provide basic industrial hygiene service to private industry.

Broader Goals

The targets and goals of industrial hygiene have undergone an evolution. Criteria of injury have become more critical and more discriminating, with radiation leading the way in establishing such remote measures of effect as the shortening of longevity and genetic effects.

I predict: Industrial hygiene will have a greater interest in detecting not only overt injury, but will necessarily explore the factors aggravating such conditions as the degenerative diseases normally present in the population, particularly the factors that influence the productivity and the general well-being of employed people.

Much more sophisticated techniques and measures of effect will be required. I believe the major fruitfulness of industrial hygiene will continue to be in the modification of environmental factors rather than in attempting to develop a more resistant man through special kinds of medication and special diet. Morbidity and mortality data will be collected and analyzed with better techniques, and will become a regular part of our program for testing the efficacy of our preventive measures.

Functional physiological tests that reveal early absorption and responses, which are clearly and readily reversible, will play an increasing part in our

surveillance program. The quality of toxicological procedures will improve greatly and ultimately will provide a reliable means for extrapolating from lower animal to man.

In spite of the successes, the rapidly changing science and technology of industry, as well as the insistent demand for lower and lower exposures (as more sensitive and more discriminating measures of effect are developed), will require an ever-greater industrial hygiene effort—far beyond our 1989 target!

Government Legislation

Legislation and extension of control through governmental rules and codes—the recent Walsh-Healey proposal for health and safety is an example—will continue to be a major stimulus to the expansion of industrial hygiene. With radiation protection and the registration and exhibition of competence required of personnel responsible for installation and operation of radiation sources, we have moved one step further in requiring in-plant health supervision than occurs with other hazardous agents.

I predict: A continuing procession of laws and codes with at least minimum standards for health and safety. To achieve compliance, industry will greatly broaden its capability and performance in providing a reasonably safe and healthful work environment. In fact, the on-the-job period will increasingly become the safest and healthiest component of the worker's life.

While government requirements will supply a base, a minimum standard, the job will be most effectively done by industrial hygienists working in and as an integral part of the industrial organization.

Better Teamwork

The teamwork approach, involving the many disciplines under laboratory, field, and clinical experiences, has been an outstanding characteristic of industrial hygiene.

I predict: We will find much better ways to achieve effective collaboration, not only within the profession of industrial hygiene, but with all other involved disciplines. The job will not be easy, for increasing specialization encourages fragmentation. At the same time, the problems become more diverse and complicated, demanding study by newer techniques and in greater depth, resulting in further specialization.

In addition, sometimes there has been a line of demarcation between the industrial hygienist in industry and his colleague in government. We shall need the very best of our joint efforts, in a climate of mutual trust and active cooperation.

This association will become a stronger stabilizing force, encouraging the specialization essential to the solution of problems. At the same time, with a clarity of focus and a resolute dedication to our basic objective—a safe and healthful occupational environment for our nation's workers—the association will provide the unifying influence so vital to the achievement of that goal.

HEADACHES IN EXPLOSIVE MAGAZINE WORKERS

D. C. Trainor MB ChM FRCSE FRACS and R. C. Jones BSc, Sydney, Australia,
Arch Environ Health 12(2): 231–234, Feb 1966.

The headache, from which many explosive workers suffer, has come to be tolerated in industry with good nature, just as seasickness is regarded (by those who do not suffer from it) as a somewhat comical ailment.

A review of 12 cases of sudden death among explosives workers by Carmichael and Lieben and reports of earlier cases by von Oettingen make one wonder whether the absorption of nitroglycerin and ethylene glycol dinitrate, even in minimal doses, does not deserve more serious consideration.

This study arose from an investigation of an explosive magazine where the men complained that their habitual headaches had become worse. We felt that the headaches were due to the fact that much more explosive was stored in the magazine than had previously been the case.

The onset of headache would occur soon after entry into a magazine and would increase in intensity during the short working period inside. Some workmen found it necessary to leave the magazine and seek relief in the open air.

It occurred to us that there existed here a situation with the following conditions:

1. The exposure was intermittent.
2. The exposure could be so arranged that it would be entirely by inhalation.
3. The concentrations of nitroglycerin and ethylene glycol dinitrate in air could be accurately measured and checked against symptoms.

4. The conditions were such that the symptom threshold could be compared with the maximum allowable concentration (MAC). This comparison was the basis of our investigation.

Environmental Conditions

The magazines are of brick construction measuring 43 feet by 26 feet, set into the side of a hill and ventilated by roof and wall-set natural draft vents. When opened, additional ventilation is supplied by the entrance doorway, two windows on the side of the porch, and one window in the rear. Operating instructions at the magazine state that the magazines should be opened at the start of the working day and remain so for an hour before entry is made. However in practice this is not done and the magazine is normally opened and the men enter immediately and commence work.

Investigations

Preliminary—Air sampling was by impingement into ethyl alcohol and resultant analyses by the phenol disulfonic acid method for nitrates. The results were calculated as milligrams of nitroglycerin per cubic meter of air. Subsequent reference to the concentration of nitroglycerin and ethylene glycol dinitrate (NG and EGDN) will be as mg NG/cu m.

The atmosphere in six magazines was examined in order to evaluate the average concentration of nitroglycerin in air to which the men were subjected.

With ambient temperatures ranging from 59 F to 61 F the concentrations of NG ranged from 0.10 to 0.53 mg/cu m giving a mean concentration of 0.36 mg/cu m. The range of concentrations could be ascribed to the amount of explosive in storage and to the length of time the magazine had been opened.

In order to ascertain whether there was any significant change in the blood pressures of eight men while at work, as compared with the blood pressure of the men after a weekend off work, their pressures were taken on a Thursday afternoon and again before commencing work on the following Monday morning. Though all but one complained of varying degrees of headache while at work there was no significant difference in the two sets of blood pressure readings.

With the onset of warmer weather, a magazine, which the workmen regarded as being "bad," was tested and six volunteers (including the authors) went into the magazine.

The reactions of the subjects are set out in Table 1 and are of some interest.

Controlled—On the magazine site there is an isolated room 25 feet by 20 feet which is used for the examination of defective explosives. To obtain a range of concentrations of NG, explosives were laid out on a table in this room on a Friday afternoon and left there till the following Monday morning to achieve equilibrium.

After several trials a quantity of explosive was selected, which, it was estimated, would give an air concentration of something under MAC.

Ten volunteers were assembled immediately on their arrival for work and their blood pressures taken. After entering the room, they were asked to remain until the headache (if any) became bad. If no severe symptoms developed within 25 minutes (the period of air sampling), the men were to leave the room and have their blood pressures taken. At the time the blood pressures were taken the men were asked to describe their symptoms. A throbbing headache was taken to mean the typical "nitro headache." Other descriptions were just as the men gave

TABLE 1.—The Effect of Exposure at Accepted MAC *

Subject	Blood Pressure Before Exposure (mm Hg)	Blood Pressure After Exposure (mm Hg)	Headache (Minutes to Develop)
1.	105/70	90/60	2
2.	100/68	90/60	2
3.	120/80	120/90	No headache Not susceptible
4.	150/90	120/70	3
5.	130/55	120/75	1
6.	120/70	110/70	2

* NG concentration 2.0 mg/cu m. Temperature = 80 F.

them for it is difficult to assess the degree objectively. The results are shown in Table 2.

With the idea of varying the concentration of NG a larger quantity of explosive was laid out in a similar manner and the tests repeated. The results are shown in Table 3.

Comment

Nitroglycerin and ethylene glycol are the nitric esters of tri and dihydric alcohols. Both have characteristics common to other members of the series in being powerful vasodilators and in being used extensively as explosives. Their physiological effects are considered to be due to the formation of nitrites.

Subjectively the most noticeable effect of absorption of either of these compounds is headache of a pulsating and very distressing nature.

The effects of nitroglycerin in the treatment of angina are well known. It causes arterial dilatation and lowering of the blood pressure. Coronary blood flow is increased and the burden on the heart is reduced.

The question of tolerance is one of some importance. There is some experimental evidence to show that tolerant animals destroy nitroglycerin less rapidly than those not habituated to it. Assuming that this is so in man, it would appear to be a sound reason for selecting "tolerant" employees for situations where exposure is likely to cause hypotension and headache.

TABLE 2.—The Effect of Exposure at a Concentration of 0.7 mg NG/cu m *

Subject	Blood Pressure Before Exposure (mm Hg)	Blood Pressure After Exposure (mm Hg)	Symptoms
1.	105/72	80/60	Headache
2.	125/100	100/85	Slight headache
3.	120/90	120/90	Slight headache
4.	130/90	120/90	Dullness (not amounting to headache)
5.	120/75	90/70	Pulsating feeling in head
6.	120/85	120/82	Slight dullness
7.	120/75	105/75	Headache
8.	125/90	100/80	Dullness
9.	130/100	100/75	Dullness
10.	115/85	95/65	Dullness

* Time in room 25 minutes. Range of concentration of NG 0.65-0.74 mg/cu m. Temperature=74 F.

TABLE 3.—The Effect of Exposure at a Concentration of 0.5 mg NG/cu m * †

Subject	Blood Pressure Before Exposure (mm Hg)	Blood Pressure After Exposure (mm Hg)	Symptoms
1.	105/70	90/55	Slight dullness
2.	135/100	115/85	Headache
3.	125/90	120/90	Slight dullness
4.	120/70	110/70	Very slight dullness
5.	160/100	150/90	No headache (not normally susceptible)
6.	130/80	105/80	Transitory headache
7.	100/75	108/70	Very slight headache

* Time in room 25 minutes. Range of concentration of NG 0.67-0.40 mg/cu m. Temperature=66 F.
† Owing to a lower ambient temperature the mean concentration of NG/cu m was somewhatlower than planned.

Mention has already been made of a number of sudden deaths among explosives workers. The fact that these deaths occurred in workers who had been 24 to 48 hours away from their customary exposure (most of the fatalities happened on a Monday morning or after a holiday) has not been adequately explained. A number of deaths happening under similar circumstances 25 years ago has also been reported.

Prolonged exposure to ethylene glycol dinitrate or to nitroglycerin will cause methemoglobinemia but it would be unlikely that this would occur to any great extent in ordinary conditions in industrial exposure. It has been suggested, however, that there may be a direct toxic action on the heart and this possibility is supported by the investigations of Suwa, et al. who found electrocardiographic changes in rabbits injected with nitroglycol. These effects passed off in 24 hours but reappeared when the rabbits were reexamined by the anoxia test method. These investigators suggest that latent toxic effects on the heart may remain after the nitroglycol has been excreted.

Lowered cerebrospinal pressure is known to be an accompaniment of the fall in blood pressure caused by these vasodilators, and it may be an important factor in causing headache.

Discussing the effect of nitroglycerin in Christmas Disease, suggests that hypotension accompanied by a lowered cerebrospinal pressure might cause a minute vascular leak from an intracerebral vessel, to assume dangerous proportions in one in whom the hemostatic mechanism is defective.

Conclusions

Although we have a certain body of proved information about the effects of nitroglycerin and ethylene glycol dinitrate, there is much about them which is speculative, and there can be no doubt that when they have been absorbed to a point where they produce headache and lowered blood pressure, their physiological action has commenced. The question arises as to whether toxic substances should be permitted to exert physiological effects of which the end results are unknown. It is our opinion that they should not.

Because of the exigencies of the work situation our investigations were carried out on a small group of men but we feel that our results are valid for the reason that the subjects were unselected. Absorption was entirely by inhalation and neither the subject nor the investigators knew during the tests what order of atmospheric concentrations was present. For this reason we consider that our findings were completely objective. It was our original intention to extend these investigations so that a larger range of exposures could be equated to blood pressures and subjective symptoms. We found, however, that there was a definite limit beyond which the Australian workman would not suffer headache in the cause of scientific investigation.

Summary

A group of six volunteers submitted themselves to an atmosphere in which nitroglycerin and ethylene glycol dinitrate were present at the maximum allowable concentration (MAC) of 2 mg/cu m. Five of the men showed a fall in blood pressure and developed marked headache within three minutes.

Ten volunteers inhaled an atmosphere in which there was a mean concentration of 0.7 mg/cu m for 25 minutes and all showed a fall in blood pressure and developed slight headache.

Seven volunteers were similarly subjected to an atmosphere in which the mean concentration was 0.5 mg/cu m and all developed mild headache and had a fall in blood pressure within 25 minutes.

It is considered that the level at which physiological response to nitroglycerin and ethylene glycol dinitrate occurs is considerably below the figure of 2 mg/cu m and that for this reason the MAC requires revision.

RESERVE SECTION

LET'S LOOK AT YOUR RECORD

Each year Reserve Medical Officers write or call the Bureau of Medicine and Surgery asking two questions.

1. Why wasn't I promoted?
2. What should I do to enhance my chances?

The key word is PARTICIPATION as actively as possible in the Naval Reserve Program and then a little more for good measure. The following points are absolutely essential.

1. Be in an active status (off the Inactive Status

List for one full year). This means being in the Selected Reserve or the Ready Reserve. If you joined the Standby One (S1 Category) after 31 July 1965 you cannot earn retirement points (BuPers Manual Article H-1404, Change 12) and thus are unable to earn a satisfactory or qualifying year.

2. Be a member of a drilling unit or in an appropriate duty status (with or without pay) or attend NROS school.

3. Take 14 days ACDUTRA each year. This can be split but remember the second tour will be without travel and allowances. It is possible that funds for ACDUTRA for Senior Officers in a District may be limited or unavailable. Don't be discouraged by this. The Bureau of Naval Personnel has offered help to support ACDUTRA in selected cases but you must let the Naval Reserve Division, Bureau of Medicine and Surgery, know of your problem so that proper support can be given to your request. It is well to remember and it is a distinct advantage, when and where feasible, to take your ACDUTRA in an environment related to your MOB billet, thus familiarizing yourself with your billet. This duty is invaluable to you.

4. Take a correspondence course. Courses are listed in the Naval Reservists, Bureau of Medicine and Surgery News Letter and in BuPers Instruction 1570.4A, Enclosure 7. Remember the course you take must be in consonance with your designator as noted in the table given in the last mentioned source of available courses.

5. Acquire the necessary 50 points for a qualifying or satisfactory year. If you wonder how many points you have earned and the number of satisfactory years, the Reserve Officer Recording Activity (RORA), Omaha, Nebraska, will supply this upon request once a year.

6. Attend Naval Reserve Medical Seminars. You may have to do it in a non-pay status if you want 14 days ACDUTRA in addition. If you go in a pay status the number of days duration of the seminar will be subtracted from the 14 days allowable (example — Seminar 4 days duration — this leaves 10 days available for second tour of ACDUTRA). Remember you can receive travel and allowance only once.

7. Reply to all official correspondence promptly. It only takes a few minutes to fill out your Annual Qualifications Questionnaire and not much longer to reply to a letter. Failure to reply gives the impression that you have lost interest in the Reserves.

8. Keep up your Post-graduate education.—Reserve Division, BuMed.

EDITORIAL DESK

APPLICATIONS FOR RESIDENCY TRAINING

The Professional Advisory Board will meet during July or August 1966 to consider requests for residency training commencing in July 1967. Applications from medical officers desiring consideration should be submitted in accordance with BUMED INSTRUCTION 1520.10C, through proper channels, to arrive in the Bureau prior to 1 July 1966. Applicants for outservice training may contact the institution and obtain tentative acceptance pending final approval by the Professional Advisory Board; however, no firm commitment should be made. Applicants are normally notified of their selection or nonselection within 30 days after the selections have been made.—Training Branch, BuMed.

PRACTICING OPTOMETRIST RECEIVES NAVY COMMENDATION

LCDR George M. Cohen MSC USNR, practicing Optometrist, Gloucester, Massachusetts received a Letter of Commendation from the Commanding Officer, U.S. Naval Hospital, Chelsea, Massachusetts on February 16, 1966.

This Commendation was given in recognition of Dr. Cohen's outstanding services rendered to the hospital during the past nineteen years where he has served as a Consultant.

The Commendation reads in part, "for your unselfish dedication, your devotion to duty and loyalty to this hospital during the past nineteen years, I hereby extend my deepest gratitude for a job 'Well Done'."

The Letter was presented by CAPT Tracy D. Cuttle MC USN, Commanding Officer, U.S. Naval Hospital, Chelsea, Massachusetts. — News Release No. 4-66, U.S. Naval Hospital, Chelsea, Massachusetts.

ACADEMIC ACHIEVEMENT OF MSC OFFICERS

The following MSC Officers were awarded the Bachelor of Arts Degree by the George Washington University on 21 February 1966:

NNMC LT Aubin H. Lovin MSC USN

NNMC LT William C. Parrish MSC USN—Technical Information Officer, NNMC, Bethesda, Md.

THE 1966 NORMAN A. WELCH MD, MEMORIAL AWARD

The Memorial

The 1966 Norman A. Welch, MD, Memorial Award will be presented by the National Association of Blue Shield Plans to the author of the most scholarly and meritorious contribution to the literature of medical economics. The work can be an article or a series of articles, a book, or a speech published or presented between July 1, 1965, and June 30, 1966. The sole criterion in judging will be the merit of the work.

The Award

A medallion of solid gold emblazoned with a bust of Dr. Welch will be awarded to the author. In addition, $1,000 will be contributed in the author's name to the Norman A. Welch Memorial Fund of the American Medical Association Education and Research Foundation. This fund is used to guarantee loans to medical students.

The Judging

The award winner will be selected by a three-man committee composed of representatives of the American Medical Writers' Association, American Medical Association and the board of directors of the National Association of Blue Shield Plans. The literature to be judged will be compiled by the library of the National Association of Blue Shield Plans. Authors wishing to submit entries may do so by sending three copies of their work to: Norman A. Welch, MD, Memorial Award, National Association of Blue Shield Plans, 425 N. Michigan, Chicago, Illinois 60611. Deadline for submitting entries is September 1, 1966.

The Presentation

Announcement of the winner and presentation of the award will be made at the 1966 Annual Program Conference of the National Association of Blue Shield Plans in Chicago on October 10, 1966.

Winner of the 1965 award was Herbert E. Klarman, Ph.D., professor of Public Health Administration at Johns Hopkins University, for his book *The Economics of Health.*

ADMIRAL McDONALD REELECTED PRESIDENT NAVY MUTUAL AID ASSOCIATION

The Board of Directors of the Navy Mutual Aid Association at their Annual Meeting on 24 February 1966 announced the reelection of ADM David L. McDonald USN, as President. Other officers elected by the membership were RADM A. H. Van Keuren USN, Ret., First Vice President; VADM V. R. Murphy USN, Ret., Second Vice President; LGEN R. C. Mangrum USMC, Third Vice President; VADM K. K. Cowart USCG, Ret., Fourth Vice President; and, CDR F. H. O'Connell MC USN, Vice President-Medical Director.

Elected to the Board of Directors were:
RADM L. A. Bachman USN, Ret.
ADM Arleigh Burke USN, Ret.
RADM J. J. Fee USN
MGEN P. J. Fontana USMC
RADM H. J. Goldberg SC USN
RADM J. B. Heffernan USN, Ret.
CAPT. J. W. Higgins, Jr., USN
RADM A. C. Husband CEC USN
CAPT S. H. Kinney USN
RADM W. I. Martin USN
BGEN Louis Metzger USMC
CAPT G. D. O'Brien USNR
RADM W. H. Schleef SC USN
VADM B. J. Semmes, Jr., USN
RADM A. M. Shinn USN

The Board of Directors reappointed CAPT T. M. Davis USN, Ret., as Secretary and Treasurer, and LCDR M. E. Koepke MSC USN, Ret., as Assistant Secretary and Treasurer.

VADM V. R. Murphy USN, Ret., was continued in office as Chairman of the Finance Committee; VADM K. K. Cowart USCG, Ret., as Chairman of the Membership Committee; and, RADM L. A. Bachman USN, Ret., as Chairman of the By-laws Committee.

The Chase Manhattan Bank of New York was continued as investment counsel for the Association and the Morgan Guaranty Trust Company of New

York retains custody of the Association's securities. The actuarial firm of Bowles, Andrews & Towne of Richmond, Virginia, will continue to serve as the Association's actuarial advisor.

CAPT Davis reported that membership increased to over 47,000 members in 1965 and the Association's assets totaled $84,813,541 on 31 December 1965. The Association earned 4.43% on its invested assets in 1965 after deducting all investment expenses.—Navy Mutual Aid Association, Washington, D. C.

BATTLEFIELD CORPSMAN

Da Nang, Vietnam (NAVNEWS) . . . . On a battlefield in Vietnam .30 and .50 caliber weapons sing a duet of death. Mortars and rockets are symbols in the cacophony. The scene appears to be one of complete pandemonium, out of the din is heard the cry, "Corpsman!"

Everyone there who hears the cry knows, for certain, two facts. One is that a Marine is wounded; the other is that within moments a Navy hospital corpsman will come running across the explosive battlefield to tend the wounded man.

Affectionately called "Doc" by the Marines with whom he serves, the corpsman is a vital, integral part of every Marine infantry platoon in combat. "If I had to choose between the two," one case-hardened sergeant said, "I'd take the doc along and leave the ammo at home."

To his Marine platoon, the corpsman is Albert Schweitzer, the Mayo Clinic and Florence Nightingale, all rolled into one. Back at the base camp, he passes out aspirin, takes temperatures and leads the patients into the doctor's office. But on patrol or other operations, he is a grizzly among bears.

For some inexplicable reason, he is presumed to be heroic . . . although that word would embarrass both him and his platoon. In the midst of a fire fight the Marine rifleman is firing from whatever protected position available or, if an advance is indicated, moves under the covering fire of others. Not so with the corpsman.

When the cry for a corpsman comes, he leaves his position instantly and dashes across the bullet-rent hill or rice paddy to find the wounded man. He kneels, cooly, and disregards the existing dangers while he tends the wounded man. He then passes the word back to radio for a Med-Evac (medical evacuation) helicopter and, picking up his medical kit, runs to the next casualty.

He is expected to disregard his personal safety, to expose himself to enemy fire in the pursuit of his profession. If he were less than heroic in combat he would be unwelcome in the outfit.

"Sure, the docs have a dangerous job," a rifleman said, "War ain't no game, you know! Matter of fact, they ought to give everyone of them a decoration the first time he comes off a battlefield. It's for sure he's earned it."

But if all are not decorated, each is given something just as tangible and much more valuable: respect. If the corpsman thinks a man should be evacuated due to a wound or illness, the company or platoon commander usually says, "Well, if the doc thinks we should, we'll do it."

Any combat Marine in Vietnam is confident of several things, each immensely comforting to him. One is that if he gets hit he will not be left behind, no matter how pressing the circumstances. Another is that weather permitting, and regardless of dangers involved, a Med-Evac helicopter will soon be there to pick him up. And, finally, he knows that neither hell nor Viet Cong will prevent an immediate response to his cry of "Corpsman!"

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ASSIGNMENT VIETNAM

Navy Medical Officers are not fully cognizant of the increased requirements placed on the Bureau of Medicine and Surgery by the escalation of the war in Vietnam.

There are currently 112 General Medical Officers, 61 Specialists, and 22 Flight Surgeons serving in Vietnam, with many new billets being written to meet the requirements of our growing commitment in Southeast Asia. With few exceptions, all of these Medical Officers were taken from the shore establishment, thereby compounding an already existing shortage.

Those who were ordered to Vietnam to meet our initial requirements have served well and are nearing the end of their one year tour, therefore they must be replaced.

The bulk of those officers who either volunteered or were ordered to Vietnam to meet our immediate requirements received orders with virtually no lead time. In fact, many were participating in a large scale Marine maneuver on the West Coast, Operation Silver Lance, and were augmenting units of the FIRST Marine Division when they were diverted to Vietnam.

The billet requirements are now essentially stabilized and BUMED is striving to issue orders several months in advance of reporting dates to allow ample preparation for overseas movement.

Billets soon to be available include duty with the FIRST and THIRD Marine Divisions, the G4 400-bed advanced base hospital in DaNang, the USS REPOSE, MILPHAP Teams (Military Provincial Hospital Assistance Program), and many more.

BUMED is strongly desirous of having as many volunteers as possible to fill these billets in Vietnam. Officers wishing to volunteer should do so by submitting an official letter request via their commanding officers with the endorsement to include a statement on the availability of the officer and whether a contact relief is required.—Medical Corps Branch, BuMed.

RECOMMENDED READING

Verbal Eccentricities in Scientific Writing, Lois DeBakey, Ph.D., The New England Journal of Medicine 274:437–439, February 24, 1966. Excellent advice for anyone interested in scientific writing, even if this is confined to hospital records.—Editor.

FOOD SANITATION

Chapter 1 of the MANUAL OF NAVAL PREVENTIVE MEDICINE (NAVMED P–5010–1) was recently revised and distributed to the field. This chapter, entitled "Food Sanitation," represents many months of researching current literature, liaison with other Bureaus and the Marine Corps, and consultation with the Public Health Service to present this definitive publication dealing with a most important subject.

Outbreaks of food-borne illness in Navy and Marine Corps general messes, both ashore and afloat, have increased during the past several years. Epidemiological investigations have revealed that a majority of all reported outbreaks of food-borne illnesses are the result of gross deficiencies in food-service sanitation, and therefore could have been prevented by strict adherence to high standards of food and general mess sanitation. Medical officers and Medical Department personnel should familiarize themselves with this chapter on "Food Sanitation." Only when faulty sanitation practices are discovered and corrective action is initiated can this rising rate of food-borne illnesses be checked.

Chapter 1 is comprised of nine sections. The ninth section contains a review of the chapter as well as a list of all references reviewed and used in the revision of the chapter.

The following is a brief summary of the various sections.

Section I enumerates responsibilities connected with food-service operations. Structural standards for food-service facilities are described. Also described are methods for procuring and inspecting subsistence items for Armed Forces. A list of definitions of words and terms used throughout Chapter 1 appears at the end of Section I.

Section II discusses standards for equipment and utensils used in food-service facilities. Dishwashing methods, dishwashing agents, and sanitizing agents used in disinfection are described, along with automatic, cold-water glasswashers and an article on plastic dinnerware. Methods for cleaning and sanitizing galley equipment and utensils are prescribed with a note of caution regarding the use of hazardous metallic coatings on galley utensils and containers.

Section III deals with the sanitary requirements and controls for milk and milk products as promulgated by SECNAV Instruction 6240.4 series. A description of the various types of milk in use, instructions for performing delivery inspections, and required temperatures for storage and serving are contained in this section. Also included are procedures for laboratory examination of milk and milk products and instructions for the proper handling of ice cream and ice cream mixes. The perishability of milk and milk products is a most important factor, thus strict compliance with all sanitary requirements is mandatory to prevent any outbreak of food-borne illnesses attributed to milk and milk products. Inspections required by the receiving activity are also discussed in this section.

Section IV discusses the various types of inspections required of subsistence items. The only inspection required to be performed by the medical officer or his representative is a delivery inspection to assure fitness for human consumption. This section also discusses the way to inspect meat and poultry; fish and shellfish; fruits and vegetables; canned products; butter, cheese, and eggs; and dry subsistence items. Inspection tips and hints are included to assist the inspector in assuring that food is safe for human consumption. Reproductions of the various inspection stamps are shown in Section IV. Much space is alloted to the inspection of fresh fruits and vegetables since these products may be procured locally and must be inspected.

Section V contains information regarding the storage and care of subsistence items. It is essential that all foodstuffs be stored in the recommended manner and in accordance with the *Bureau of Supply and Accounts Manual.* Section V discusses the storage and care of non-perishable subsistence items and fresh and frozen subsistence items. Also discussed in this section are the sanitary precautions to be observed in the handling and procurement of ice in food-service operations.

Section VI deals with sanitary precautions that must be observed when preparing and serving food in order to prevent outbreaks of food-borne illnesses. The majority of food-borne illnesses can be traced to one or more of the following:

a. Food that has been prepared far in advance of serving;

b. Inadequate refrigeration;

c. Disregard of the time and temperature factors; or

d. Food-service personnel who were ignorant of or careless in applying the recommended food handling techniques.

Food must be prepared and served as recommended in this section. Protein foods which are not served immediately after cooking must be either chilled to a temperature of 40° F. or lower, or held at a temperature of 140° F. or higher. These foods, if held longer than three hours between 40° and 140° F., shall be considered unsafe for human consumption and shall be destroyed. This section discusses the proper way to prepare and serve chilled foods, ground foods, meats, fresh vegetables, frozen foods, reconstituted dehydrated foods, sandwiches, and pastries. Also discussed are the recommended practices regarding salad bars; self-service items; express serving lines; clubs, messes, and exchanges; mobile canteen trucks and vending machines; and coffee messes.

Section VII discusses health standards for food-service personnel. This section discusses the added importance in connection with the present program of procuring contract food-service personnel to work in general messes. Food-service employees must have physical examinations prior to commencing work and must be examined regularly thereafter. Food-service personnel who have open lesions on the hands, face, or neck shall be prohibited from performing food-service duties.

Section VIII contains complete information on investigating and reporting food-borne illness outbreaks. Chapter 23 of the *Manual of the Medical Department* and other directives require that a special epidemiological report (MED 6200–2) be submitted by dispatch to the Bureau of Medicine and Surgery by any ship or station immediately upon the occurrence of five related cases of enteric disease, including food-borne illness, in any 48-hour period.

Many food-borne illness outbreaks go unreported. The Bureau of Medicine and Surgery cannot take action to aid field activities unless outbreaks are reported and can be studied to determine remedial methods and courses of action to be transmitted back to the field. An example of this was recently demonstrated through reporting of shigella outbreaks on certain ships of the guided missile cruiser class during the past several years. The Bureau of Medicine and Surgery conducted an analytical survey of these outbreaks and learned that faulty eductor systems aboard these ships created a back-up of sewage which subsequently led to the shigella outbreaks. Working closely with the Bureau of Ships and the office of the Chief of Naval Operations, BUMED has been able to institute action which will correct the faulty eductor systems on the ships concerned during their overhaul periods.—PrevMedDiv, BuMed.

DEPARTMENT OF THE NAVY

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